Develop New or Improved Approaches for Preventing or Delaying the Onset or Progression of Disease and Disability

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Lowering Mother-To-Child Transmission of HIV Through Cesarean Delivery

Background: Mother-to-child (vertical transmission) of the human immunodeficiency virus type-1 (HIV) is a global problem of immense proportions. Worldwide, an estimated 500,000 children became infected with HIV in 1998, primarily because of transmission of the virus from their mothers during pregnancy or shortly after. A substantial proportion of cases of vertical transmission of HIV occur around the time of delivery, when maternal vaginal fluids come in contact with the newborn. Therefore, performing a cesarean section before the onset of labor and before the rupture of membranes could decrease the risk of vertical transmission. Results of previous studies to address the issue of whether mode of delivery is associated with the risk of transmission had yielded conflicting results.

Advance: An international collaborative effort to evaluate the association between mode of delivery and the risk of vertical transmission of HIV was initiated by NIH using a meta-analysis (systematic methods to search, combine and evaluate previous research data and findings). This collaboration involved the NIH and CDC as well as representatives of fifteen cohort studies from the U.S. and Canada and Europe. The results of this study indicated the risk of transmission of HIV from mother to child was approximately 50% lower among women who delivered via cesarean section, before onset of labor and rupture of membranes, compared to women who delivered by other means. The likelihood of transmission was further reduced, by approximately 87%, when cesarean section was performed before labor and rupture of membranes, along with using antiviral drugs (such as zidovudine).

Implications: Based in large part upon the results of this study, the American College of Obstetricians and Gynecologists- Committee on Obstetric Practice has recommended that HIV-infected women be offered cesarean section delivery before labor and rupture of membranes to further reduce the risk of vertical transmission of HIV, beyond that achievable with antiviral drugs alone.

The International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1: a meta-analysis of 15 prospective cohort studies. N Engl J Med 340: 977-987, 1999.

American College of Obstetricians and Gynecologists. Scheduled cesarean delivery and the prevention of vertical transmission of HIV infection. ACOG Committee Opinion 219: Washington, D.C., 1999.

Pharmacological Gene Therapy for X-linked Adrenoleukodystrophy

Background: X-linked adrenoleukodystrophy (X-ALD) is a genetic disorder that affects the nervous system, the adrenal gland, and the testes in an estimated 1 in 20,000 individuals. Individuals with this disorder have impaired capacity to degrade very long chain fatty acid (VLCFA)--a component of specific foods that are high in fat and cholesterol-- resulting in its accumulation in the body. In children, X-ALD may lead to severe disability and often death before ten years of age. Those with a less severe form of X-ALD, which mainly involves the spinal cord, may survive to old age. While adrenal insufficiency responds readily to replacement therapy and testicular changes rarely cause symptoms, there is no good treatment for the disorder=s impact on the nervous system. Current therapies, which include bone marrow transplantation, and dietary therapy with a mixture of glyceryl trioleate and glyceryl trierucate (referred to as Lorenzo=s Oil), have not been consistently effective. The deficient X-ALD gene, which has recently been mapped to chromosome Xq28, encodes a peroxisomal memebrane protein (ALDP) which is part of a small family of related proteins involved in fatty metabolism. Because of this defective gene, peroxisomes (organelles that are involved in degrading VLCFA) function improperly.

Advance: Investigators demonstrated that a chemical, 4-phenylbutyrate (4-PBA), improved the capacity of cells from X-ALD patients to lower the levels of VLCFA by turning on a Aredundant gene.@ Redundant genes are similar genes that can completely or partially substitute for the functions of the other gene (in this case, the defective gene). These genes are candidates for a novel, pharmacological approach to gene therapy that is based on turning on a similar, underexpressed gene within the organism, rather than the traditional gene therapy approach of introducing a normal copy of the defective gene from another organism.

To determine if 4-PBA increases peroxisome growth, researchers examined cells from X-ALD patients that were treated with 4-PBA and compared them to those that had not been not treated. The study revealed a 2.4-fold increase in the number of peroxisomes in treated cells, leading to an increase in an ALD related protein named ALDRP. This related protein (ALDRP) was encoded by a redundant geneBa gene from the same Afamily@ as ALDP. Since ALDRP has previously been shown to be able to substitute for the action of ALDP in cell cultures, the investigators hope that 4-PBA could be developed as a genetic medicine because of its capacity to turn on a redundant gene.

Implications: These research findings suggest that using 4-PBA to activate redundant genes may potentially prevent or treat the severe neurological abnormalities observed in X-linked adrenoleukodystrophy. This type of pharmacological gene therapy could also have clinical application in treating disorders related to the peroxisomes, as well as other inborn errors of metabolism. [secondary B treatment]

Kemp S, Wei HM, Lu JF, Braiterman LT, McGuinness MC, Moser AB, Watkins PA, and Smith KD: Gene redundancy and pharmacological gene therapy: Implications for X-linked adrenoleukodystrophy. Nature Medicine 4: 1261-68, 1998.

Hypothyroidism During Pregnancy Linked to Lower IQ for Child

Background: The thyroid gland is found in the neck and produces hormones important for protein synthesis in virtually every body tissue and is also vital for increasing the cell=s use of oxygen. Hypothyroidism is a condition where the gland does not produce enough hormones, resulting in fatigue; coarse, brittle hair; thick, coarse skin; and a lowering of the body=s metabolic rate. But, in many cases, the disorder goes undetected because there are no obvious physical signs or symptoms. When hypothyroidism occurs simultaneously in a pregnant woman and her fetus, the child=s neuropsychological development may be adversely affected.

Advance: In a recent retrospective study, researchers determined that children born to mothers with untreated hypothyroidism during pregnancy scored significantly lower on IQ tests than children of healthy mothers. The children ranged from 7 to 9 years at the time of the study and participated in a series of psychological tests relating to intelligence, attention, language, reading and school problems, and visual-motor performance. In these children, 15% had IQ scores lower than 85, compared to only 5% of the control children. Overall, the affected children scored poorer on all 15 individual tests than the children born to healthy mothers. Of the 62 women in the study who had hypothyroidism, 48 did not receive treatment during pregnancy for their condition. Of their children=s IQ scores, 19% were below 85. However, the children born to mothers who had received treatment scored similarly to the control children, suggesting that treatment can help lessen the adverse effects.

Implications: This study suggests that hypothyroidism might be added to the group of correctable maternal conditions that can influence the long-term health of the child. Hypothyroidism can be determined by measuring thyroid stimulating hormone (TSH) levels in the blood. High TSH levels serve as an early warning that the thyroid is not functioning adequately. The condition can then be treated with medication (thyroid hormone). These findings suggest that early detection and treatment for hypothyroidism of the mother during pregnancy might be an important factor in the intelligence and well-being of her child. Additional research is needed to form the basis for maternal screening policies.

Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O=Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, and Klein, RZ: Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. New Engl J Med 341: 549-555, 1999.

Planet Health: A Successful Obesity Intervention Among Youth

Background: The prevalence of obesity among children and youth in the United States has increased rapidly over the past 30 years, making it the most common nutritional disorder among these age groups and a major cause of excess medical problems and death later in life. Although the origin of obesity is complex and relates to both genetic and environmental factors, obesity ultimately results from too much food intake for calories burned. Since the imbalance of caloric intake and expenditures involves the choice of voluntary behaviors (such as watching television or eating high fat food whose prevalence has skyrocketed in children), these behaviors were chosen as targets for new intervention programs. Targeting these and other factors, investigators enrolled 1300 students in the 6th and 7th grades from 4 public schools in a 2 year, school-based intervention program called Planet Health. Taught through regular classes, the intervention focused on decreasing television viewing, decreasing consumption of high-fat foods, increasing fruit and vegetable intake, and increasing moderate and vigorous physical activity. The intervention was also designed to be interdisciplinary, use school resources efficiently, and target all students, not just the obese ones. Control schools received their usual health curricula.

Advance: After 2 years, the prevalence of obesity among girls in intervention schools was significantly reduced from 24% to 20% compared with control schools in which it *increased* from 22% to 24%. No significant differences were found among boys, in which obesity declined in both the control and the intervention schools. Over the 2 years, the intervention significantly reduced television hours among *both* girls and boys, and increased fruit and vegetable consumption. In girls, reduced television viewing was associated with a reduced prevalence in obesity in the study population. There were also changes in obesity noted by ethnic group: the largest decline in obesity was seen among African American girls; the decline among White girls was similar to the average for all participants, with no change among Hispanic girls.

Implications: Because the risk of adult obesity is increased if one is significantly overweight during adolescence, interventions to reduce obesity among young children and adolescents are particularly important. The data confirmed the potentially important role of television viewing time in changing obesity in teens and indicated that a focus on reducing television viewing time can be a useful addition to school-based intervention efforts. Investigators hypothesize that the success of the program among girls is probably due to the fact that girls may be more attuned to issues of diet and activity and thus more responsive to the intervention. Alternatively, the fact that boys in both intervention and control schools lost weight implies that different factors may affect weight control in boys. The success of this program in public schools, implemented by regular classroom and physical education teachers, also indicates that this promising approach to reducing obesity can be widely adopted.

Gortmaker SL, Peterson K, Wiecha J, Sobol AM, Dixit S, Fox MK, and Laird N: Reducing obesity via a school-based interdisciplinary intervention among youth. Arch Pediatr Adolesc Med 153: 409-418, April 1999.

A*Going Places*@ Promise in Preventing Problem Behavior

Background: Adolescent problem behaviors, including substance abuse, school misconduct, precocious sex, and aggressive behavior, are associated with a range of social and health problems such as school failure, incarceration, and injury. Problem behavior is relatively rare among preadolescent children. However, the prevalence of problem behaviors increases dramatically during adolescence among both males and females in all socioeconomic strata. Poor adjustment to the unique demands of early adolescence contributes to the likelihood of early initiation of problem behavior.

To address these issues, researchers developed a program called A*Going Places*.@ *Going Places* is a school-based intervention program targeting problem behaviors among middle-school students. The program targets adolescents= social skills and personal responsibility through classroom, parent, and school environment components. Seven middle schools in one suburban school district are participating in this research project, with three schools implementing the *Going Places* program and four schools providing data to be used for comparisons. All students in the district completed questionnaires prior to the implementation of the curriculum in the fall of grade 6. Surveys are completed annually in the spring of grades 6, 7, and 8.

Advance: This research is ongoing, but preliminary analyses indicate the program is having positive effects. Compared with students not in the program, students exposed to the program for two years were significantly less likely to smoke, engage in aggressive or deviant behavior and had fewer friends who engaged in problem behaviors. In addition, participating students had less positive expectations regarding cigarette use, and perceived that fewer other students used tobacco and alcohol. Finally, participating students retained a more positive perception of their school climate, perceived their parents as knowing more about them, and reported less increase in parent-adolescent conflict than non-participants.

Implications: These interim results suggest that a prevention program targeting social skills may be effective in addressing adolescent behaviors and attitudes associated with poor social and academic development, and may curtail involvement in behaviors that put adolescents at risk. This program is unique in that it addresses protective and risk factors common to many problem behaviors. Thus, *Going Places* has promise as a research-based prevention program targeting multiple problem behaviors among young adolescents.

Simons-Morton B, Crump AD, Haynie DL, Saylor KE, Eitel P, and Yu K: Psychosocial, school, and parent factors associated with recent smoking among early adolescent boys and girls. Preventive Medicine 28: 138-148, 1999.

Simons-Morton B, Haynie DL, Crump AD, Saylor KE, Eitel P, and Yu K: Expectancies and other psychosocial factors associated with alcohol use among early adolescent boys and girls. Addictive Behaviors 24: 229-238, 1999.

Simons-Morton B, Crump AD, Haynie DL, and Saylor KE: Student-school bonding and adolescent problem behavior. Health Education Research Theory and Practice 14: 99-107, 1999.

Identifying Contributors to Infant Homicide

Background: Homicide is the leading cause of infant death due to injury in the U.S. Infants are more likely to be killed than older children, possibly because of their behavior, such as crying and physical vulnerability. Earlier reviews of case fatality records have shown that more than 80% of infant homicides were considered to be child abuse by medical examiners and other case reviewers. These studies had also found that although the mother is more likely to commit these acts during the first week of the infant=s life, the majority of infant deaths *after* the first week of the infant=s life were caused by males.

Advance: Using data from linked birth and death certificates from 1983-91, researchers found that one-fourth of murdered infants were killed by the second month of life; one-half by the fourth month, and two-thirds by the sixth month. During the nine year period of the study, medical examiners or coroners identified about 2,800 U.S. infants as homicide cases, about one a day. Based on studies of under-reporting of infant homicides, researchers surmised that about twice the amount of infant homicides actually may have been committed during that same time period compared to what was reported. Furthermore, comparison of data from the earlier and later periods of the study, and to more recent data, indicates that rates of homicide have not decreased and may, in fact, be increasing.

Researchers also found that the likelihood of being killed was greatest for the second or later born child of a teenage mother. These infants were about ten times more likely to be killed than the first child of the oldest mothers. A mother=s lack of a high school education and no prenatal care were also risk factors. Even when the researchers excluded infants of the youngest teen mothers from those whose mothers were old enough to complete high school, infants of mothers with only a high school education were still eight times more likely to be killed than infants of mothers who completed college. Information on fathers of the infants was missing in about 40% of the homicides.

Implications: The timing of these deaths indicates that interventions which teach behavioral skills and provide social support to teenage mothers are needed prior to the birth of the infant. In previous studies of nonfatal child abuse, interventions which used professional nurses who visited the homes of the mothers both prenatally and for two years after the child=s birth were found to protect first-born children from abuse. Given that nearly 500 serious injuries occur from child abuse for every homicide case, researchers emphasize that early interventions for both fatal *and* nonfatal child abuse are desperately needed.

Overpeck MD, Brenner RA, Trumble AC, Trifiletti LB, and Berendes HW: Risk factors for infant homicide in the United States. N Engl J Med 339: 1211-16, 1998.

Brenner RA, Overpeck MD, Trumble AC, DerSimonian R, and Berendes H: Deaths attributable to injuries in infants, United States, 1983-1991. Pediatrics 103: 968-974, 1999.

Treatment of Bacterial Vaginosis May Not Prevent Preterm Birth

Background: Bacterial vaginosis is found in 15 - 30% of U.S. women, making it the most common vaginal infection. In many previous studies, pregnant women who had this condition were at increased risk of giving birth to a premature infant. Based on this information, some prominent clinicians have recommended that all pregnant women be screened for bacterial vaginosis, and those who have it be treated, to prevent premature birth. However, there have been no randomized clinical trials to indicate that treating bacterial vaginosis in pregnant women actually prevents premature delivery. Since bacterial vaginosis is very common, a policy of mass screening and treatment would mean that several hundred thousand pregnant women might be exposed to antibiotics each year, with no guarantee of benefit.

Advance: Researchers screened pregnant women for the presence of bacterial vaginosis during the second trimester. Women who had bacterial vaginosis were randomized to receive either metronidazole (the drug of choice for treating bacterial vaginosis), or identical-appearing placebo capsules. They then compared the occurrence of premature birth in the treated group with the occurrence in the placebo group.

The occurrence of premature birth did not differ significantly between the 966 women in the treated group and 987 in the placebo group. Premature birth occurred to 12.2% of women in the treated group and 12.4% in the placebo group. Furthermore, there were no significant differences between the groups in low birth weight, very low birth weight, premature labor, premature rupture of the membranes, or maternal or neonatal infections. This was in spite of the fact that treatment was effective at eradicating the bacterial vaginosis.

Implications: These results imply that although bacterial vaginosis has been consistently associated with an increased risk of preterm birth, treatment of this condition will not reduce preterm birth. These results also tell us that much more research is needed before we understand the mechanism of the association between vaginal infections and prematurity. This study has immediate implications for public health. Were it not for these convincing results, hundreds of thousands of pregnant women might have been exposed to a powerful antibiotic without any prospect of benefit, adding unnecessary costs to the health care system.

Klebanoff MA and Carey JC, for the NICHD MFMU Network: Metronidazole did not prevent preterm birth in asymptomatic women with bacterial vaginosis. American Journal of Obstetrics and Gynecology 180: S2, 1999.

Progress in Developing Vaccines Against Infectious Diseases in Children

Background: Despite impressive progress in vaccine development over the last decades, millions of children around the world are still affected by infectious diseases that are either unique to specific regions or even epidemic. One such disease is shigellosis, also known as bacillary dysentery. The bacteria that most commonly causes this form of dysentery is *Shigella dysenteriae* type 1. This antibiotic-resistant organism produces a protein toxin (shiga toxin) that is responsible for the most serious complication of *Shigella* infectionBhemolytic uremic syndrome (HUS). HUS is potentially fatal in children, causing kidney failure and severe, irreversible damage to other organs.

Advance: Using techniques they pioneered to make effective vaccines against many bacterial diseases, researchers have been leading efforts to produce an effective vaccine against shigellosis. Specifically, the researchers have chemically linked sections of a bacterium=s surface that alone do not provoke an immune response to harmless proteins that *do* stimulate an immune response. (The goal of vaccine development is to stimulate the body=s immune response so that antibodies may be mobilized). In addition, because vaccine production usually involves growing large quantities of dangerous bacteria, these scientists have also been developing synthetic vaccines by making synthetic polysaccharides of the same composition as those on the surface of the bacteria and linking them to proteins. Preliminary tests have validated this approach for vaccine production because it yields higher potency vaccines against shigellosis and can be more consistently controlled than vaccines derived from bacteria.

Implications: Since there are no valid animal models for studying shigellosis, developing an effective mechanism of protection against the disease has been difficult. Furthermore, until now, many experts had believed that a vaccine against shigellosis would not prevent *Shigella dysenteriae* from growing in the bowel. The development of a vaccine against *Shigella dysenteriae* has disproven this assumption and opens the door for vaccines against closely related pathogens such as *E. coli O157*, a bacteria which infects meat and is responsible for thousands of sometimes fatal infections each year, mainly in vulnerable children. Most importantly, millions of children who will benefit from this advance could be protected from shigellosis and other devastating childhood infections.

Poszsgay V, Chu C, Pannell L, Wolfe J, Robbins JB, and Schneerson R: Protein conjugates of synthetic saccharides elicit higher levels of serum IgG lipopolysaccharide antibodies in mice than do those of the O-specific polysaccharide from *Shigella dysenteriae* type 1. Proc Natl Acad Sci: 96: 5194-5197, 1999.

Robbins JB, Schneerson R, Bryla DA, Trollfors B, Taranger J, and Lagergard T: Immunity to pertussis: not all virulence factors are protective antigens. In: Gupta S, Sher A, Ahmed R, eds. Mechanisms of lymphocyte activation and immune regulation VII. Plenum Press: New York, 207-218, 1998.

Recruitment of Young Urban Black Men to Clinical Trials

Background: Young urban black men comprise an at risk population for several conditions. Because of social, psychologic, economic and educational factors in their lives, they may not engage in health promoting behaviors. Many do not have access to a primary care provider and have no or limited health insurance. An important goal of health care is developing a means of maintaining connectedness to this population. The study recruited and followed a sample of underserved, inner-city, hypertensive, young black men. Then an educational intervention was used by a nurse-community health worker team in combination with usual medical care. The educational intervention incorporated individualized counseling, monthly telephone calls and a home visit. A control group received usual medical care alone.

Advances: The study collected important information about the factors influencing how/why young urban black men seek care, remain in care and follow treatment plans. The study also showed the success of different methods of recruitment from a variety of sources. Importantly, the educational-behavioral intervention delivered by the nurse-community health worker teams resulted in excellent return of people for hypertension care follow up visits.

Implications: The results of this study can be extended to other hard-to-reach populations who are at risk for poor health outcomes. Those hard-to-reach populations include high risk pregnant women, frail elderly, those with chronic disease and developmentally disabled individuals of all ages. The success of the tested intervention which established the provider-patient relationship has implications for other populations who report negative experiences receiving primary care in emergency departments or the disruption of continuity by different providers and different systems for each encounter.

Hill MN, Bone LR, Hilton SC, Roary MC, Kelen GD, Levine DM: A clinical trial to improve high blood pressure care in young urban black men. American Journal of Hypertension 12:548-554, 1999.

Determining Accurate Placement of Feeding Tubes

Background: Each year in the U.S. there are about one million patients or nursing home residents who are tube-fed. A common event in any care setting, including in the home, is displacement of the feeding tube from its proper location. Either upon insertion of the feeding tube or at any time after insertion, there is potential for the tube=s location to be displaced such that tube feeding contents may be directed into the respiratory tract. That event is potentially fatal and, at best, results in morbidity and additional health care costs.

Current clinical methods that do not utilize x-rays to determine the placement of feeding tubes are accurate from 6 to 34% of the time. X-rays of the abdomen are the most accurate determination of correct placement, and are often required by policy upon insertion or reinsertion of a feeding tube before tube feedings can begin. However, movement by the patient or transfer of the patient from bed to chair, or unknowing removal of a feeding tube by the patient himself, may require x-rays with each subsequent event of full or partial dislodgement in order to ascertain correct placement of the reinserted or repositioned feeding tube. The current study evaluated a new, noninvasive method of verifying correct feeding tube placement by using limited chemical analysis. The analysis was performed on aspirated material once a feeding tube has been inserted/replaced.

Advance: The study validated a method of estimating placement of feeding tubes by determining pH and bilirubin levels in the aspirated contents from a feeding tube. The combination of pH levels and bilirubin levels resulted in the correct identification of all instances of improper placement of the feeding tube into the respiratory tract. Similarly, correct placement in either stomach or intestines was identified correctly in most instances.

Implications: The study developed and validated a method to determine proper placement of feeding tubes that is quicker and less costly than the current use of x-rays. The study method identified all instances of placement of the feeding tube in the respiratory tract, an event which has consequences of high morbidity and mortality. The study method saves costs of x-rays, as well as attendant discomfort to the patient.

Metheny NA, Stewart BJ, Smith L, Yan H, Diebold M, Clouse RE. pH and concentration of bilirubin in feeding tube aspirates as predictors of tube placement. Nursing Research 48:189-197, 1999.

Women=s Cardiovascular Risk Factors on the Job

Background: Since the 1970s, studies of the effects of physical activity on health focused initially on men and how active they were on their jobs. These older studies found sudden death to be much more common among sedentary workers compared to more active workers. Eventually, studies also focused on leisure-time activity, assuming that leisure time, rather than occupational work time in a sedentary role, provided the major chance to reduce cardiovascular risk. Studies have also shown positive effects of leisure-time activity on reducing women=s cardiovascular risk. Despite this information, many women do not participate in leisure-time vigorous activity. Some women also do not exercise much at work because their job is sedentary and provides little opportunity to exercise. The current study examined women=s energy expenditure at work and their patterns of cardiovascular risk.

Advance: Women in different occupational groups were analyzed to see how much energy they spent at work. The study showed that women at the greatest cardiovascular risk may be those women who couldn=t move about much on the job or didn=t participate in vigorous physical activity outside of work. This study discovered that cardiovascular benefits may come from even small amounts of energy expended on the job, even if women don=t exercise much at home or during their leisure time.

Implication: Employment policies which provide incentives to increase physical activity, especially among women, may result in improved cardiovascular benefits as well as improved morale and reduced health care costs in the short and long term. This study suggests that such incentives include: rewarding those who increase their exercise at work, promoting walking up and down stairs instead of using elevators, promoting walking instead of sit-down breaks and others which cost employers little. Together, this study=s findings may help women feel more in charge of their health.

Wilbur J, Naftzger-Kang L, Miller AM, Chandler P, Montgomery A: Women=s occupations, energy expenditure and cardiovascular risk factors. Journal of Women=s Health 8:377-387, 1999.

Health-Promotion Behaviors of Black and White Caregivers

Background: This study focused on caregivers and how they attain and maintain their own health and well-being. The work of caregivers continues to provide quality of life, literally, to millions of individuals who may be frail, old, or impaired in several important areas of life, including in thinking and performing activities of daily life. Several health-affecting behaviors of caregivers, themselves, have been identified: exercise, intake of alcohol, smoking, use of medications and others. This study identified specific patterns of health promotion associated with African-Americans caregivers compared to white American caregivers.

Advance: The study affirmed that caregivers were interested in promoting and protecting their health. The study also discovered different patterns of health-promoting behaviors of black caregivers compared to white caregivers. Black caregivers used a greater reliance on spiritual/religious activities, avoided drugs and alcohol, and closely followed the advice of health professionals. Among white caregivers, there was greater reliance on keeping active/staying busy and volunteering for others.

Implications: Most patients and their families want to do all they can to keep frail, disabled, demented or otherwise impaired individuals at home in their community. Differentiating between successful approaches used by black and by white caregivers is a first step toward individualizing interventions that enable caregivers to continue in their role, and to remain healthy with high quality of life.

McDonald PE, Fink SV, Wykle ML. Self-reported health-promoting behaviors of black and white caregivers. Western Journal of Nursing Research:538-548, 1999.

Simple Lifestyle Changes Can Boost Physical Activity and Cardiovascular Health

Background: Lack of physical activity is a major risk factor for heart disease and contributes to other illness as well. About one-quarter of U.S. adults are sedentary, and another third are not active enough to reach a healthy level of fitness. The federal government recommends that adults try to get at least 30 minutes of moderate-intensity physical activity on most, and preferably all, days of the week. However, many Americans fail to achieve this goal because of lack of time, social support, and access to exercise facilities, along with bad weather and a dislike of vigorous exercise.

Advance: A recent study showed that incorporating physical activity into an individual=s lifestyle is an effective alternative to a structured, gym-based exercise program. In this study, 235 sedentary adults were divided into two exercise groups. Participants in the structured program received a prescription for 20 to 60 minutes of exercise 3 to 5 days a week on equipment at a fitness center; participants in the Alifestyle@ program were advised to accumulate at least 30 minutes of moderate-intensity physical activity most days in whatever way they could. Both groups learned behavioral skills to help them be physically active, but participants in the Alifestyle@ program received more individualized help to tailor their physical activity changes to their daily routines. Such lifestyle changes included taking longer walks on the way to office meetings; walking around airports, instead of sitting while waiting for a plane; walking around a soccer field at children's games; and forming a walking club. Over 2 years, both activity groups had significant improvements in physical activity and fitness, and both had significantly lowered blood pressure and body fat. No real differences between the two groups could be shown.

Implications: Changing from a sedentary lifestyle to an active one is estimated to cut the risk of developing cardiovascular disease in half. This study shows that people have more opportunities to add physical activity to their daily life than they might think. By incorporating the results of this research into their daily lives, Americans can immediately begin to improve their health and cardiovascular disease risk.

Dunn AL, Marcus BH, Kampert JB, Garcia ME, Kohl HW, Blair SN: Comparison of lifestyle and structured interventions to increase physical activity and cardiorespiratory fitness: A randomized trial. JAMA 281:327-334 1999.

Researchers Discover How Long HIV Can Survive in Drug Paraphernalia

Background: Specific information about how long HIV can survive in drug paraphernalia, such as the syringes, cookers, water and filters that are typically used by injection drug users has long been needed. (Cookers are used to dissolving the powder form of drugs, such as cocaine and heroin, into an injectable form.) Knowing the survivability of the virus in the paraphernalia will be particularly useful as health professionals work to develop more effective HIV prevention efforts to stop the viral transmission.

Advance: Using a variety of laboratory simulations and newly developed microculture assays researchers were able to determine the duration of survival of HIV in the syringes and cookers used typically by injectors of illicit drugs. HIV was found to survive for periods in excess of 4 weeks in blood within the lumen of the syringe. Syringes with detachable needles were found to harbor more blood between their plunger and base, indicating that they may be riskier for HIV transmission than syringes with needles that do not detach. The likelihood of encountering a potentially infectious syringe decreased with time but remained finite for an extended period. Survival of the HIV in the cookers was found to be dependent on the temperature achieved during preparation of drug solutions. HIV was found to be inactivated once the temperature exceeded on average 65^{O}C. Heating the cookers for 15 seconds or longer reduced viable HIV below detectable levels.

Implication: The biological reality that HIV can survive and possibly be transmitted over a 30-day period through contaminated syringes supports the public health rationale for HIV prevention strategies that target injection drug users. Also knowing the protective effect of heating drug solutions for at least 15 seconds to inactivate HIV virus is a straightforward message that the prevention community can use to prevent further spread of HIV in drug users who continue to inject.

Clatts MC, Heimer R, Abdala N, Goldsamt LA, Sotheran JL, Anderson KT, Gallo TM, Hoffer LD, Luciano PA, and Kyriakides T. HIV-1 transmission in injection paraphernalia: heating drug solutions may inactivate HIV-1. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology in press.

Abdala N, Stephen PC, Griffith BP, and Heimer R: Survival of HIV-1 in syringes. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology 20:73-80, 1999.

Maternal Smoking During Pregnancy Increases the Risk that Offspring Will Have Conduct Disorders, ADHD and Will Use Drugs

Background: Over the years there has been much speculation about the long-term health and behavioral effects of children born to mothers who smoke during pregnancy. Several recent studies have found a relationship between maternal smoking during pregnancy and psychopathology in the offspring, particularly attention-deficit/ hyperactivity disorder (ADHD) and conduct disorder (CD). Because of the numerous confounding factors, such as differences in socio-economic status, level of education, parenting problems, and possible differences in the prevalence of psychopathology between women who smoke during pregnancy and those who do not, it remains difficult to firmly establish a causal association. Most studies do include controls for some of these factors, but few have ascertained psychiatric diagnoses of the parents. Childhood and adolescent psychopathology, including ADHD and CD prominently, have been implicated as possible factors in the development of substance use and abuse. None of the maternal smoking studies to date have followed offspring to the age when drug use onset is most likely to occur.

Advance: In a 10-year longitudinal study, researchers found that female offspring of mothers who smoked 10 or more cigarettes per day during pregnancy were 5 times more likely to develop drug abuse or addiction during adolescence than were offspring of mothers who did not smoke during pregnancy. Among boys, maternal smoking during pregnancy was associated with a 4-fold increase in the risk of conduct disorder. Although fathers married to women who smoked during pregnancy were more likely to be alcohol abusers than were fathers married to women who did not smoke during pregnancy, analyses showed that this could not account for the difference in drug abuse in girls or CD in boys. These findings also could not be explained by maternal drug or alcohol abuse during pregnancy, parental psychiatric diagnosis, family risk factors, prenatal and early developmental history of the offspring, postnatal maternal smoking, or smoking in the offspring.

Implications: These findings of increased rates of drug addiction among adolescent girls whose mothers smoked during pregnancy indicate a group at high risk for substance abuse. In addition, the findings are consistent with the working hypothesis that nicotine exposure during critical developmental periods may predispose the brain to subsequent addictive influences because of its effect on the dopamine system, though the gender difference remains to be explained. Clinically, the findings underscore the need for smoking prevention and cessation programs in women during pregnancy.

Weissman MM, Warner V, Wickramaratne PJ, Kandel DB. Maternal smoking during pregnancy and psychopathology in offspring followed to adulthood. Journal Of The American Academy of Child and Adolescent Psychiatry 38(7) 892-899, 1999.

Cost Effective Addiction Prevention Program for Rural Families

Background: Parents can play a critical role in combating adolescent drug abuse. Research has shown that family-based prevention interventions that focus on improving parents' communication and disciplinary skills can help children avoid drug use. These family interventions, though effective, can be costly to implement on a long-term basis. A short-term family intervention for general populations called Preparing for the Drug Free Years (PDFY) has been developed that is designed to enhance general parenting skills and discourage child drug abuse.

Advance: Recently, two studies were conducted to determine the effectiveness of PDFY in rural family settings. PDFY uses five, two-hour, weekly sessions to teach parents how to establish and maintain rules, to be positively involved with the child, and to manage conflict and anger. Parenting behaviors improved in all families that participated in the PDFY program.

Implications: As one of the first empirically validated, low cost family interventions to produce positive outcomes, the program shows great potential for application to communities around the country. The general nature of this program does not stigmatize families and has broad appeal for parents, especially when their children are entering vulnerable transition periods, like middle or junior high school.

Spoth R, Redmond C, Shin C, Lepper H, Haggerty K, and Wall M: Risk moderation of parent child outcomes in preventive intervention: a test and replication. American Journal of Orthopsychiatry, 68(4): 565-579,1998.

Breast Cancer Risk Reduced in Women at Inherited Risk for the Disease Who Choose Prophylactic Surgery

Background: Our understanding of the genetic factors that influence breast cancer risk continues to improve. Through research studies, we have discovered that certain alterations in the *BRCA1* or *BRCA2* genes or a family history of breast cancer markedly increases a woman=s risk for the disease. Today, when a woman is faced with the knowledge that she has an inherited predisposition to breast cancer her choices include close observations to ensure early detection, prevention with tamoxifen, or prophylactic surgery to remove breasts and/or ovaries before disease develops. While data suggests that tamoxifen may lead to a 49 percent reduction in the incidence of primary breast cancer in women at a high risk for the disease, little data is available on surveillance and prophylactic mastectomy interventions. Despite this lack of scientific data, some women who are at high risk of breast cancer make the difficult decision to have both breasts surgically removed, a procedure known as bilateral prophylactic mastectomy (PM).

Advance: Two recent studies provide some exciting new information on prophylactic surgery in the reduction of breast cancer risk in women at high risk for the disease. Researchers studied the long-term outcomes of PM surgery in women with a family history of breast cancer who had undergone PM at the Mayo Clinic between 1960 and 1993. In this study, PM was associated with a reduction in incidence of the disease of at least 90 percent.

In a separate study, researchers explored whether prophylactic oophorectomy (PO)Bsurgical removal of the ovariesBlowers the risk of breast cancer among women at inherited risk of breast and ovarian cancer due to *BRCA1* mutations. This study compared the incidence of breast cancer in women with *BRCA1* mutations who had undergone PO with that of women with similar mutations who had not had a PO. PO was found to reduce the risk of breast cancer by about 40 percent for all women with *BRCA1* mutations and that risk reduction increased over time from surgery. Prophylactic removal of the ovaries has been recommended for women at inherited risk of breast and ovarian cancer on completion of the woman=s childbearing years to decrease the risk of ovarian cancer. This data provides additional information on the use of PO in reducing the risk of breast cancer in this population of women at high risk.

Implications: These studies are of major importance to the health care of women at markedly increased risk of breast cancer due to an inherited mutation of *BRCA1* or a family history of the disease. Together these studies add to our body of knowledge on reducing the risk of breast cancer among women with a genetic predisposition to the disease. While these findings are provocative, further research is needed to replicate these findings and to explore other aspects of prophylactic surgery, including optimal surgical techniques, hormone replacement and the use of preventive agents following surgery, and the public health implications of these interventions among targeted risk groups.

Harman LC, et al.: Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. New England Journal of Medicine 340(2):77-84, 1999.
Rebbeck TR, et al.: Reduction in breast cancer risk after bilateral prophylactic oophorectomy in *BRCA1* mutation carriers. Journal of the National Cancer Institute 91(17):1475-1479,1999.

Tamoxifen Reduces Breast Cancer Risk in Women at High Risk

Background: Breast cancer is the most common cancer in women, and the second leading cause of cancer death. In 1999, an expected 175,000 women will be diagnosed with breast cancer, and approximately 43,300 women will die of their disease. In 1992, the NIH-supported National Surgical Adjuvant Breast and Bowel Project (NSABP) implemented the precedent-setting Breast Cancer Prevention Trial (BCPT) to see whether the drug tamoxifen prevents breast cancer in women who are at an increased risk of developing the disease because of age or personal or family history. Tamoxifen (Nolvadex7, Zeneca Pharmaceuticals, Wilmington, Del.) had been used since the 1970s to treat breast cancer.

Advance: Researchers on the BCPT demonstrated a 49 percent reduction in breast cancer incidence among the high-risk participants who took tamoxifen, a drug used for the past two decades to treat breast cancer. Women on tamoxifen also had 50 percent fewer diagnoses of noninvasive breast cancer, such as ductal or lobular carcinoma in situ. Tamoxifen did increase the women's chances of three rare but life-threatening health problems: endometrial cancer (cancer of the lining of the uterus); pulmonary embolism (blood clot in the lung); and deep vein thrombosis (blood clots in major veins).

Researchers are now creating and testing a second generation of breast cancer prevention agents, such as raloxifene, which may help to reduce the risk of the disease without some of tamoxifen=s potential side effects. In 1999, the NSABP launched the Study of Tamoxifen and Raloxifene (STAR), a trial that is comparing the two drugs= abilities to reduce the frequency of the onset of breast cancer in high-risk, post-menopausal women, as well as comparing the side effects of the two drugs. Approximately 22,000 women will participate in this important study.

Implications: The results of the BCPT provide evidence that the risk of human cancer can be reduced with a pharmacologic intervention (in this case, tamoxifen). The BCPT also showed that large chemoprevention trials can accrue participants and be completed successfully. The study=s findings provide an alternative to Awatchful waiting@ or surgery for women who are at high risk of developing breast cancer; this challenges health care providers involved in the care of breast disease to develop a better understanding of risks and benefits in healthy populations and to be able to counsel "at-risk" women regarding available options.

Fisher B, Costantino JP, Wickerham DL, et al.: Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. Journal of the National Cancer Institute 90: 1371-1388, 1998.

Depression in Adolescence

Background: Every adult remembers that adolescence is marked by rapid emotional, intellectual, and physical change, so when a teenager seems depressed, parents, schools, and health providers often attribute the signs of depression to Ajust a phase the teen is going through@ and expect her or him Ato grow out of it.@ However, many teenagersBat any given time, about 4-6% of all adolescents in the U.S.Bdo suffer from major depression, which may lead to suicide, impair development and quality of life, cause conduct problems, and, in some cases, be related to violent behavior, such as recent school shootings. Although conclusive data has not been gathered, it has been suspected that many adolescents who experience depression will later suffer from depression as adults. Tragically, we have not understood the full and devastating impact that depression can have on a child=s whole life.

Advance: A team of researchers, including mental health specialists, studied a group of young adults who had been diagnosed with major depression during their adolescent years, along with a group of healthy control subjects, all of whom had originally been studied 10-15 years earlier. Although only in their mid-to-late twenties, the group with major depression in adolescence had a high rate of suicide (7.7% compared with 0% for the controls); five times the risk for suicide attempts; and twice the risk of another occurrence of major depressionBalthough there was no increased risk for other mental disorders. The adults who were depressed as adolescents were more likely to have been hospitalized for psychiatric or medical reasons and to be impaired in work, social, and family life.

Implications: Major depression has generally been considered an adult illness, but this study shows that depression that begins in adolescence is likely to continue into adulthood and often leads to suicide, suicide attempts, or a high degree of long-term disability. With this awareness, it becomes critically important that depression among adolescents is detected early and treated appropriately.

Weissman MM et al.: Depressed adolescents grown up. JAMA 281: 1707-1713, 1999.

Exploring Psychosocial Treatments for Depressed Adolescents

Background: For many years, major depression was thought to affect only adults. The full range of treatments that we now haveBmedications and psychotherapiesBwere developed for, and proven useful in, depressed adults. We now understand that many adolescents also suffer from major depression and know that, for these teens, depression can lead to drastic life-threatening actions, such as suicide or violent behavior; impair development and quality of life; cause conduct problems; and increase the likelihood the teen will experience recurring depressions as an adult. It is critically important that depressed adolescents be treated promptly and with treatments that are both age-appropriate and effective. Unfortunately, there is little data on what treatments work for adolescents. Some types of antidepressant medications (tricyclics) do not seem to work for this age group, although other types (serotonin uptake inhibitors) do, if used properly. Several recent studies have shown that certain forms of group or individual psychotherapy, such as cognitive behavioral therapy, can help adolescents. This preliminary work suggests that another type of psychosocial treatment, interpersonal psychotherapy (IPT), can also be effective for adolescent depression.

Advance: In the first controlled study of the efficacy of IPT for adolescents, forty eight adolescents with major depression were randomly assigned to two groups. These adolescents were between 12 and 18 years old, lived in New York City, and were primarily Latino girls from low socioeconomic status families. The teens in one group received interpersonal therapy adapted for adolescents (IPT-A) weekly for 12 weeks, while those in the other group received clinical monitoring with limited therapy for the same time period. In addition, members of both groups were able to call upon their therapists to some extent between sessions, if they felt worse. At the end of the 12 weeks, 75 percent (18) of the group receiving IPT-A had recovered from their depression, compared to 46 percent (11) of those in the clinical monitoring control group. Approximately twice as many teens in the IPT-A group remained in treatment for the entire period as did those in the control group.

Implications: This study, although limited in numbers of participants, indicates that IPT-A, like cognitive behavioral therapy, can be an effective treatment for adolescents with depression B as it is for adults. IPT-A also appears to be acceptable to teens in this age group and with this social and cultural background since so many remained for the duration of the study. This form of psychotherapy could become an important approach for reducing depression among adolescents.

Mufson L et al.: Efficacy of interpersonal psychotherapy for depressed adolescents. Arch Gen Psychiatry 56: 573-579, 1999.

Young People are Most Susceptible to Panic Disorder

Background: People with panic disorder experience unexpected and repeated episodes of intense fear accompanied by physical symptoms that may include chest pain, heart palpitations, shortness of breath, dizziness, or abdominal distress. A panic attack often mimics the symptoms of a heart attack or other life-threatening medical condition, necessitating the immediate use of extensive and costly medical procedures to rule out these conditions before the panic disorder is diagnosed correctly and treated properly. Often, people with panic disorder develop other anxiety disorders such as phobias, which further restrict and impair their lives.

In the early 1980s, a large surveyBthe ECA (Epidemiologic Catchment Area) survey B estimated that about 1.7 percent of U.S. adults, approximately 2.4 million peopleBhave panic disorder in any given year, with women twice as likely as men to develop the disorder. This measurement zeroed in on the magnitude of this mental disorder across the nation, but left many unanswered questions, such as how many of the people experiencing panic disorder each year represent new, and how many repeat, cases or what the natural progression of the disorder is likely to be in these individuals.

Advance: In 1981, the original ECA survey interviewed approximately 3500 people living in BaltimoreBone of 5 different cities in the study. About 12 years later, almost 2000 of these same people, or 73 percent of the survivors, were interviewed again. The interviews at both time points required each participant to undergo a standard diagnostic test to detect any current or previous mental disorders. In the intervening years, new cases of panic disorder occurred at a rate of 1.43 cases per 1000 people per year. The incidence was greater in females than males; in fact, 31 of the 35 new cases were in women. The incidence rate also declined with age: it was 3.43 cases (per 1000 people per year) for ages 18-29 years, 2.32 for ages 30-44, 0.61 for ages 45-64, and 0 for people over 65 in this group. Over half the people with new cases of panic disorder had a pre-existing anxiety of some sort for many years before the onset of the panic disorder.

Implications: This study tells us that panic disorder is most apt to begin when a person is young and suggests that it may often, but not always, be an outgrowth of a pre-existing anxiety the person has. Panic disorder only rarely begins after mid life. Recovery is usually rapid after a full-blown episode of panic disorder, although, after the initial episode, a significant number of people continue to have frequent panic attacks for many years before undergoing a rapid recovery. It is important that people with panic disorder seek professional help so they can receive appropriate treatment, which can reduce or prevent panic attacks in 70 to 90 percent of people with the disorder.

Eaton WW et al.: Onset and recovery from panic disorder in the Baltimore Epidemiologic Catchment Area follow-up. British Journal of Psychiatry 173: 501-507, 1998.

Redefining The Need For Mental Health Care Among Older Americans

Background: Most psychiatric research to date has focused on the problems and needs of people younger than 45 years of age. While older people visit their primary care doctors more often than do younger people, they receive relatively less attention to mental health concerns. The medical literature offers very few studies that not only support the need for improved mental health care for the elderly but also clearly show what the range of problems actually are in this age group. We have little reliable information about what sorts of emotional and psychological difficulties and needs emerge among older peopleBor how medical practitioners and health care institutions should respond to those needs. In fact, there has been no carefully organized study looking at the full range of psychiatric diagnoses among the elderly.

Advance: The researchers recruited a group of 224 patients between the ages of 60 and 89 years of age, from a variety of socioeconomic backgrounds. These individuals were carefully screened for the full range of possible mental health issues and concerns, with researchers taking care to watch for the sorts of problems more apt to occur among older people, such as dementia, mood disorders, and Aoverlays@ that involve multiple medical or psychiatric diagnoses in the same patient. The psychiatric examinations, tests, and questionnaires were selected and monitored to offer a high degree of reliability in the information. And the study clearly confirmed that mental health problems are not only common among older people, but the specific nature of those problems differ from what emerges in younger individuals. Depression still ranks very high as an issue among the elderlyBbut so do dementia, alcohol abuse and dependence, and bipolar disorder.

Implications: This study responded to a pressing question: what are the actual mental health needs of people older than 60 years of age? In structuring a response to this question, researchers used the best of earlier information in combination with careful evaluation, all toward a more complete portrait of the psychological and emotional problems of older Americans. Along with a clear confirmation that psychiatric diagnoses are common among the elderly, this study reminds us that observation and management of these concerns will go far toward controlling costs of care, particularly given the very effective tools (simple but reliable in-office tests, drug therapies) now available to primary care practitioners. The researchers also clarified the need for practitioners to be more vigilant for psychological issues in the Amix@ of their older patients= problems, and laid essential groundwork for further studies that will refine the questions and further the examination of emotional needs in older peopleBand how we can best respond to those needs.

Lyness JM, Caine ED, King DA, Cox C, Yoediono Z: Psychiatric disorders in older primary care patients. Journal of General Internal Medicine 14(4): 249-254, 1999.

Lyness JM, King DA, Cox C, Yoediono Z, Caine ED: The importance of subsyndromal depression in older primary care patients: prevalence and associated functional disability. Journal of the American Geriatric Society 47:(6), 647-652, 1999.

Changing Women=s Behavior to Prevent Disease

Background: In the U.S., the groups of people likely to become infected with the HIV virus that causes AIDS have changed over past years. AIDS no longer affects primarily gay men, but is now a leading cause of premature death for American women. Approximately 20 percent of new AIDS cases are now women andBbecause infections of women continue to increaseBamong people newly diagnosed with the HIV virus, the percentage of women is even greater. Most women with HIV become infected through sexual contact and the women most likely to become infected are poor ethnic minority women. In fact, although only 21 percent of U.S. women are African American and Hispanic, approximately 77 percent of AIDS cases in women are from these minority groups.

The best way to prevent infection with HIV is by changing behavior and for women, this means changing sexual behavior. We have learned that intensive small-group interventions are successful in changing women=s= sexual behavior. However, attacking the AIDS public health epidemic calls for much larger-scale, community-level prevention approaches that can reduce risky sexual behavior for large numbers of women.

Advance: An HIV prevention trial was undertaken with almost 700 women living in 18 low-income housing developments in five U.S. cities. Women participated in activities designed to educate them about risky behaviors and how to reduce them. These activities included workshops on how to reduce the risk for HIV infection and other community HIV prevention events led by women who were popular opinion leaders among their peers. Some control groups of women did not participate in the prevention-focused activities (interventions), but were surveyed similarly to the intervention groups. The proportion of women in the intervention groups who reported any unprotected intercourse within the past 2 months declined from 50 percent to 38 percent, and the percentage of times these women had intercourse protected by condoms increased from 30 percent to 47 percent. In addition, 12 months later, the frequency of unprotected intercourse acts within the past 2 months among these women tended to be lower than when they initially entered the trial. By contrast, there was essentially no change in these risky behaviors among the women in the control groups that did not participate in the activities focused on prevention.

Implications: Prevention programs that involve and engage women from impoverished inner-city neighborhoods in neighborhood-based HIV prevention activities can bring about reductions in high-risk sexual behaviors. Although this research focused on women at risk for HIV, the intervention model can also be adapted for other population groups and other behaviors detrimental to health.

Sikkema KJ et al.: Outcomes of a randomized community-level HIV prevention intervention for women living in 18 low-income housing developments. *American Journal of Public Health*, in press, 1999.

Home Visits By Nurses When Children Are Young
Reduce Criminal Behavior In Later Years

Background: Crimes committed by children (individuals younger than 18 years of age), along with a wide variety of other antisocial behaviors among children, are on the rise, and have been for more than a decade. What lies behind this disturbing fact has been widely discussed, with little real progress in either understanding the problem or knowing what to do about it.
Children at risk are born to teenaged mothers, single mothers, substance-abusing parents, or into families already invaded by poverty, illness, or psychological difficulties. These children are often poorly prepared for making the best choices that lead to adult success, opting instead for a variety of antisocial or overtly criminal activities. Many researchers, educators, and physicians have proposed that stronger prevention efforts be focused on these children, but the question has remained: will such efforts to prevent or reduce antisocial behavior in childhood really work?
Advance: Starting in the early 1980s, researchers selected 400 pregnant women, most of them young, unmarried, and poor. During the pregnancies and after the birth of the children, nurses made home visits. Mothers were given instructions for maintaining good health for themselves and their children. They were educated about proper care of their children and family planning. Jobs were discussed and promoted for both income-producing and esteem-building purposes. Links were established between the mothers and health and human service agencies, and they were encouraged to make use of these services. Home visits continued until the children were 2 years old. 15 years later the researchers returned to talk to the mothers and their now-teenaged children, comparing them to a Acontrol group@ of mothers and children who did *not* receive home visits. They also looked at official school records and teacher=s reports, all aimed at answering the question: had those home nurse visits had a positive impact in the lives of the children?
Implications: The answer is a clear *yes*: teenagers born to the women who received the home visits had less problems. These children managed to avoid or limit their use of illegal drugs, cigarettes, and alcohol. They had fewer sexual encounters. They had fewer school expulsions, and fewer arrests for any sort of criminal activity. The home visit children still had problemsCbut they did better in responding to those problems, and tended to make more constructive and life-enhancing choices.
This encouraging study confirms that prevention *is* effective in the risk-laden lives of young, poor, disadvantaged children (and their mothers). The positive long-term benefits of those home visits of 15 years ago were clearly shown. This study emphasizes the need for greater efforts on behalf of children at risk, and underscores the positive outcomes we can expect. These investigators offer persuasive evidence that early efforts on behalf of children at riskCusing simple, inexpensive techniques like education and information, reassurance, and positive reinforcementCdefinitely work.

Olds D, et al: Long-term effects of nurse home visitation on children=s criminal and antisocial behavior: 15-year follow-up of a randomized controlled trial. Journal of the American Medical Association 280: 1238-1244, 1998.

Home-based and Group Exercise Programs Can Improve Health and Functioning of Healthy and Frail Older Adults

Background: Longitudinal analyses of aging populations have shown that it is never too late to adopt healthier lifestyles, and recommended changes, at any age, can result in more positive health outcomes. Psychologists and other social scientists, working with epidemiologists and clinicians, examined facilitators and barriers to physical activity, such as the effect of socioeconomic status, social support, and perceived efficacy. Results of these studies were used to design more effective and long-lasting strategies to help older people incorporate beneficial changes into their lifestyles. With the collaboration of behavioral scientists, researchers also started examining the effects of physical activity on a wider range of well-being and quality-of-life measures.

Advance: Recent studies examined mechanisms linking exercise and a variety of health outcomes, including cognitive functioning. The first study is seminal in its focus on neurological pathways linking exercise with cognitive functioning. Previously sedentary older adults with six months of light to moderate aerobic walking showed significant improvement in higher thinking tasks. The beneficial effect is selective; it seems to affect only those functions associated with the frontal regions of the. The second study demonstrated that community-based exercise programs can improve endurance and decrease bodily pain in sedentary healthy older adults. This is one of the first studies to document a significant decrease in bodily pain for older persons who engaged in stretching and flexibility exercise. The third study demonstrated that a home-based strengthening program for older persons resulted in significant improvements in strength, gait, and disability levels among persons with physical disability. These studies delineate the effects of different types of exercise programs (i.e., strength, endurance, balance, and flexibility) on various physical functioning and psychosocial health outcomes.

Implications: It is never too late to improve the quality of life through exercise. Researchers must continue to explore the benefits of exercise in diverse, older populations. Exercise programs for older persons can have both physiological and psychological benefits, and future research must determine and prescribe appropriate exercises for diverse older persons to obtain the maximum improvement in quality-of-life outcomes. Finding ways to promote exercise programs designed specifically for older persons holds promise as a feasible and effective public health strategy for achieving physical activity-related health benefits in the growing older population.

Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, Chason J, Vakil E, Bardell L, Boileau RA, and Colcombe A: Ageing, fitness and neurocognitive function. Nature 400 (29): 418-419, 1999.

King AC, Pruitt LA, Phillips W, Oka R, Rodenburg A, and Haskell WL: Comparative effects of two physical activity programs. Journal of Gerontology: Medical Sciences (in press) 1999.

Jette AM, Lachman M, Giorgetti MM, Assmann SF, Harris BA, Levenson C, Wernick M, and Krebs D: Exercise--it's never too late: the Strong-for-Life program. American Journal of Public Health 89 (1): 66-72, 1999.

Prediction of Healthy Aging and Disability-Free Life Expectancy

Background: There is a need to understand if there are modifiable risk factors that can decrease the risk of disability and death with aging. A long-term study with Japanese-American men in Hawaii has shown that these men have one of the highest life expectancies of all Americans. Because a number of baseline measurements were taken of these men in midlife, it was possible to explore predictors of long life expectancy and prevention of physical disability. Although, ideally, preventive measures should begin early in life, a clinical trial of various preventive measures in later life has been completed in the setting of a senior center.

Advance: Among over 6500 healthy men at baseline, about 60% remained free of major illness and were not physically or cognitively impaired over the next 25 years. Data from midlife that proved to be predictive of healthy aging included optimal blood pressure, low blood sugar and cholesterol levels, lack of obesity, lack of smoking, and strong hand grip. At an older age the men were examined to determine the presence of functional limitation and disability. Of various factors considered, midlife hand grip strength in the highest third of the distribution, when compared with the lowest, was associated with less physical disability and faster walking speed. In the clinical trial, participants were randomized into intervention and control groups. At the end of one year after a regimen of increased physical activity and chronic-illness self-management, the intervention group experienced fewer hospitalizations and fewer total hospital days.

Implications: Factors leading to a long and active life are of prime importance as the population ages worldwide. These factors can be treated. This study suggests preventive and/or therapeutic interventions need to be initiated at younger ages even though the clinical trial results suggest that successful intervention can occur at older ages.

Reed DM, Foley JD, White LR, Heimovitz H, Burchfiel CM, Masaki K: Predictors of healthy aging in men with high life expectancies. American Journal of Public Health 88: 1463-1468, 1998.

Rantanen T, Guralnik JM, Foley D, Masaki K, Leveille S, Curb JD, White L: Midlife hand grip strength as a predictor of old age disability. JAMA 281: 558-560, 1999.

Leveille SG, Wagner EH, Davis C, Grothaus L, Wallace J, LoGerfo M, Kent D: Preventing disability and managing chronic illness in frail older adults: a randomized trial of a community-based partnership with primary care. JAGS 46: 1191-1198, 1998.

Testosterone Replacement for Older Men with Low Testosterone Levels May Have Protective Effects Against Age-Related Diseases

Background: Many older men have blood levels of testosterone well below the normal range for younger men. Epidemiologic and physiologic findings suggest that low testosterone may increase risk factors for disease and disability in older men, including loss of bone (leading to osteoporosis and fractures), loss of muscle (causing decreased strength), and increases in body fat (increasing risks for diabetes and heart disease); but data from controlled trials are sparse.

Advance: In a randomized trial, 108 men over 65 years old with low serum testosterone wore a testosterone or placebo skin patch for three years. Levels of testosterone in the treatment group rose to those generally found in younger men. Bone density in hip and spine, lean and fat tissue mass, and muscle strength were measured. There were no significant treatment effects on bone density for the group as a whole. Analysis of effects in the spine, however, revealed a strong relationship between the testosterone level before starting the trial (Aendogenous@ testosterone) and testosterone therapy=s effect on bone. Men with the lowest endogenous serum testosterone (3 micrograms per liter or less) had significant increases in bone density in response to testosterone replacement, while those with higher levels did not. Testosterone treatment increased lean body tissue and decreased fat mass significantly more than placebo.

The study monitored adverse treatment effects, particularly on the prostate, since raising testosterone could increase risk for benign prostatic hypertrophy, enlargement with age of a gland in the male reproductive system, and prostate cancer. Rises in prostate-specific antigen (PSA), an indicator to do further testing for prostate cancer, were more frequent in men receiving testosterone than in controls; but the difference was statistically insignificant and the rises usually transient. One case of prostate cancer occurred (in the treatment group) but there were far too few subjects to draw conclusions about prostate cancer risk. Testosterone treatment did not increase prostatic hypertrophy symptoms, such as impaired urinary function.

Implications: These results suggest that testosterone replacement could help protect many older men with low testosterone levels against common diseases of aging such as diabetes, heart disease, and osteoporosis. However the possibility that testosterone replacement could also significantly increase adverse events such as prostate diseases, though this was not observed in this small study, reinforces the need for careful larger studies and for exploring strategies to minimize risks of testosterone therapy while still providing benefits.

Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Holmes JH, Dlewati A, Staley J, Santanna J, Kapoor SC, Attie MF, Haddad JG, and Strom B: Effect of testosterone treatment on bone mineral density in men over 65 years of age. The Journal of Clinical Endocrinology & Metabolism 84: 1966-72, 1999.

Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Lenrow DA, Holmes JH, Dlewati A, Santanna J, Rosen DJ, and StromBL: Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. The Journal of Clinical Endocrinology & Metabolism 84: 2647-53, 1999.

Insights Regarding Recommended Physical Activity for Older Persons

Background: Lower risks for diseases and death are associated with higher cardiorespiratory fitness, determined by the oxygen consumed per minute while exercising as hard as possible on a treadmill or stationary bicycle. Most people do not choose to undergo such testing, however, which is expensive and poses some risk. It would be useful for them to have an alternative way to estimate whether their physical activity levels are likely to sustain a protective level of fitness. Current guidelines to the public for aerobic exercise intensity use formulas based on heart rate as a surrogate measure for oxygen consumption. Age-related changes in cardiac and respiratory responses to exercise, however, pose the need to validate these formulas in older persons, to determine whether they provide appropriate guidance to them on how intensely to exercise.

Advance: In a large epidemiologic study of leisure time physical activity and cardiorespiratory fitness in over 13,000 men and women aged 20 to 87, researchers compared subjects with low, moderate, and high fitness. (Both the moderate and high fitness groups had substantially lower disease and mortality risk at all ages than the low fitness group.) At all ages, the average leisure physical activity in individuals in the moderate and high fitness groups was relatively modest; for the moderate group, the activity was equivalent to taking a 30-minute brisk walk most days of the week.

Another group examined the applicability to older women of current heart-rate-based aerobic exercise guidelines. These researchers measured heart rate and oxygen consumption in 112 women aged 60-72 at differing walking speeds. They found that levels of exercise that raise oxygen consumption appropriately could be selected by a conventional method (estimating maximum heart rate as 220 minus one=s age), and by exercising hard enough to produce a desired percent (typically 70) of this rate. However, they found that another common heart-rate-based approach for choosing exercise intensity, the Aheart rate reserve@ method, results in selecting too hig an intensity. (Heart rate reserve = maximum heart rate - resting heart rate).

Implications: The epidemiologic findings reinforce current public health recommendations stating that adults of all ages can derive substantial health benefits from moderate leisure physical activity. The aerobic exercise study provides reassurance that older women can use a simple heart rate-based method to select appropriate exercise intensity. However, the study=s finding that another heart rate-based method selected *inappropriate* intensity illustrates the need for this type of study to test the validity of exercise-related recommendations for older persons.

Stofan JR, DiPietro L, Davis D, Kohl HW, and Blair SN: Physical activity patterns associated with cardiorespiratory fitness and reduced mortality: the Aerobics Center Longitudinal Study. American Journal of Public Health 88: 1807-13, 1998

Kohrt WM, Spina RJ, Holloszy JO, and Ehsani AA: Prescribing exercise intensity for older women. Journal of American Geriatrics Society 46: 129-33, 1998.

Postmenopausal Estrogen Has a Positive Influence on Carotid Artery Stiffness

Background: Arterial stiffness has been identified as a potential risk factor for cardiovascular disease. Earlier research has shown that estrogen may improve blood vessel pliability by altering the structure and function of vascular tissue and smooth muscle cells. This suggests that estrogen replacement therapy (ER) should have a favorable influence on the arterial stiffening that occurs with age.

Advance: This study examined the influence of age and current estrogen replacement therapy (ERT) on stiffness in the common carotid arteries (the main arteries that pass up the neck and supply blood the head). The common carotid arteries of 172 women, 37 of whom were current users of ERT, were examined by ultrasound, and the degree of arterial stiffness was measured. Arterial stiffness was found to increase linearly with age, and was modestly related to other cardiac risk factors. The degree of stiffness was lower in women using ERT than in postmenopausal nonusers. Furthermore, the effects of age and ERT on the stiffness persisted after adjustments for other cardiovascular risk factors. Carotid stiffness was similar in ERT users, whether or not they also took progesterone.

Implications: Age-associated increases in carotid artery stiffness are reduced by postmenopausal estrogen replacement therapy (ERT). This study suggests that the cardiovascular protection seen in women using ERT may involve overall reduction of age-associated arterial stiffening. [secondary B treatment]

Nagai Y, Earley CJ, Kemper MK, Bacal CS, and Metter EJ: Influence of age and postmenopausal estrogen replacement therapy on carotid arterial stiffness in women. Cardiovascular Research 41:307-31, 1999.

Multicomponent, Targeted Interventions Prevent Delirium in Hospitalized Older Patients

Background: Delirium, also known as acute confusional state, is a common, serious, and potentially preventable source of morbidity and mortality among hospitalized older patients. It is of particular importance because patients over age 65 account for more than 48% of all days of hospital care, and the incidence of delirium will probably increase with the aging of the population. Previous intervention studies of delirium had methodological limitations and focused on the treatment of delirium rather than on primary prevention. The present study evaluated the effectiveness of a multicomponent strategy for the prevention of delirium.

Advance: This is the first large-scale clinical trial targeted toward prevention of delirium. Study participants received either usual, standard hospital care or care under a multidisciplinary team of specialists that included staff nurses, recreational therapists, physical therapists, geriatricians, and trained volunteers. The investigators targeted patients with one or more of six risk factors for delirium, including cognitive impairment, sleep deprivation, immobility, dehydration, or impaired vision or hearing. To address these risk factors, team members used targeted intervention protocols, such as work games and orientation and memory aids to sharpen thinking; relaxation tapes, massage, and warm drinks at bedtime to promote sleep; exercise to increase mobility; vision and hearing aids to improve sight and hearing; and provision of oral fluids to prevent dehydration. While 15% of patients receiving standard hospital services experienced at least one episode of delirium, only 9.9% of those receiving the team approach experienced an episode. Patients receiving the multicomponent approach experienced fewer episodes and a reduction in the number of days of delirium. The intervention did not, however, affect either the duration of hospital stay or the rate of readmission.

Implications: This controlled clinical trial provides evidence that a multicomponent, targeted intervention strategy is effective for the prevention of delirium in hospitalized older medical patients. The intervention prevented the initial development of delirium and reduced the total number of days of delirium. It was most effective in patients who were at intermediate risk of delirium at baseline. Once an initial episode of delirium had occurred, however, the intervention had no significant effect on the severity of delirium or the likelihood of recurrence. This finding has an important implication for the treatment of delirium; i.e., primary prevention is probably the most effective strategy. Once delirium has occurred, this intervention strategy is less effective and less efficient.

Inouye SK, Bogardus STJ, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, and Cooney LMJ: A multicomponent intervention to prevent delirium in hospitalized older patients. N. Engl. J. Med. 340: 669-76, 1999

Links between AIDS and Malaria: Minimizing Transmission of AIDS

Background: An estimated 14 million people in sub-Saharan Africa are infected with the AIDS virus and at least 500 million Africans suffer from malaria each year. The chance that an individual will be infected with both diseases in many parts of Africa is therefore quite high. The relationship between the AIDS and malaria infections is however unclear. A novel laboratory study shows that cells infected with the AIDS virus grew in number when exposed to the malaria pigment. The progression to the full AIDS disease following virus infection is more rapid when increased amounts of virus are found in the bloodstream. Person to person transmission of the AIDS virus is also facilitated by a higher load of the virus. This observation inspired U.S. researchers and their colleagues in Malawi to design a study in adult patients with the purpose of understanding the effect malaria has on the quantity of AIDS virus present in the bloodstream.

Advance: The study in Malawi compared adult blood donors with malaria who also had AIDS virus infection to blood donors who had the AIDS virus but did not have malaria. Individuals with malaria were treated with standard anti-malarial drugs and the amount of virus was measured in the bloodstream of both groups before and after treatment. When first measured, there was seven times as much AIDS virus in the bloodstream of patients with malaria than in those without malaria. One month later, the amount of AIDS virus in those without malaria remained unchanged. In contrast, a significant decrease was seen in the AIDS virus levels in blood donors treated for malaria. The next step will be to measure the effect of malaria on AIDS virus infection over the long term in a community with high levels of both infections to determine whether anti-malaria treatment fully reverses the effect.

Implications: Malaria prevention efforts have faltered in the last decade in part due to economic deficiencies, social disruption and the spread of drug resistance throughout Africa. The results of this study suggest that renewed malaria control efforts may be critical to slowing the progression of the AIDS in infected individuals and may reduce the rapidity of person to person transmission of the AIDS virus.

Hoffman IF, Jere CS, Taylor TE, Manthali P, Dyer JR, Wirima JJ, Rogerson SJ, Kumwenda N, Eron JJ, Fiscus SA, Chakraborty H, Taha TE, Cohen MS, and Molyneux ME: The effect of *Plasmodium falciparum* malaria on HIV-1 RNA blood plasma concentration. AIDS 13: 487-494, 1999

A Study of the Safety and Effectiveness of the Anti-AIDS Viral Drug Nevirapine in Infected Pregnant Ugandan Women and their Newborn Children

Background: Previous studies demonstrated that a short treatment with the anti-AIDS drug AZT could reduce mother-to-child transmission of the AIDS virus in Thailand among non-breast feeding mothers and to a lesser extent in Ivory Coast among breast feeding mothers. However, even short treatments with AZT are too expensive to provide to the general population by Health care systems in many developing countries. Therefore, scientists have been searching for even more cost-effective treatments using new anti-viral drugs or combinations of available drugs which could be more affordable and potentially more generally available to poorer populations in the developing world. Nevirapine was recently identified as a new drug that might achieve this objective. The advantage of Nevirapine is that the drug remains active against the AIDS virus in the body for a long time. Therefore a single dose can replace the multiple doses of AZT, a short acting drug, which are necessary to kill the AIDS virus lowering the expense for treatment.

Advance: In the initial study the safety and effectiveness of Nevirapine was tested in AIDS virus infected pregnant women in Uganda and their newborn children. Nevirapine was given as a single dose during labor to the infected women and afterward to infants born to these women. Nevirapine was well tolerated by women and infants and no serious adverse effects related to the treatment were observed. Nevirapine demonstrated potent anti-AIDS virus activity in women resulting in a significant drop in the amount of virus in their bloodstream one week after treatment. These results demonstrated that Nevirapine treatment had considerable promise to prevent AIDS virus transmission, which can occur during birth and breast-feeding. Based upon these results, a follow up study was conducted that compared the effectiveness of Nevirapine treatment to AZT treatment. The follow-up study found that transmission of the AIDS virus to newborn children was reduced by half from infected mothers with Nevirapine treatment compared to AZT treatment. Longer term studies are planned to determine the effectiveness of Nevirapine in reducing AIDS virus transmission from infected women who continue to breast feed their infants

Implications: Nevirapine is 70 times less expensive and much easier to administer than AZT. Nevirapine treatment offers the best hope to reduce mother to child AIDS virus transmission in developing countries and may be useful to further reduce mother to child transmission of AIDS in the U.S.

Musoke P, Guay LA, Bagenda D, Mirochnick M, Nakabiito C, Fleming T, Elliott T, Horton S, Dransfield K, Pav JW, Murarka A, Allen M, Fowler MG, Mofenson L, Hom D, Mmiro F and Jackson JB. A phase I/II study of the safety and pharmacokinetics of nevirapine in HIV-1-infected pregnant Ugandan women and their neonates (HIVNET 006). AIDS 13: 479-486, 1999

Progress toward Development of a Broadly Effective HIV Vaccine

Background: With HIV infection threatening to affect over 40 million people worldwide by the year 2000, and with the greatest affliction in regions and populations with highly limited health care resources, the need for a practical and effective vaccine is urgent. The existence of multiple strains of HIV, coupled with the high frequency of mutation (genetic change) characteristic of HIV, presents a major challenge to researchers attempting to develop such a vaccine. Because HIV is so highly variable, design of a broadly effective vaccine is an especially desirable objective.

Advance: Recently, researchers devised a vaccine candidate that, when tested in a mouse model, induced protective neutralizing antibodies to many strains of HIV. Their strategy builds on earlier work targeting the HIV envelope proteins (proteins located on the external membrane of the virus) that facilitate the early binding and entry of HIV to cells. However, in this case the investigators developed HIV vaccine immunogens (molecules capable of eliciting an immune response) that incorporate portions of specific HIV surface proteins that are exposed transiently during the process of binding and fusion of the virus with a target cell. Infected cells with the HIV envelope protein on their surface were isolated and mixed in culture with cells genetically engineered to have two key co-receptor molecules for the virus on their membrane surfaces. The cells were allowed to fuse together just as the virus does in the course of infecting cells. In the middle of this reaction, the cells were chemically treated to "freeze" their spatial conformation (shape), thus exposing critical regions of the HIV envelope protein that are normally hidden by the virus. This cell preparation, which the investigators termed a fusion-competent immunogen, was then injected into mice in order to generate antibodies to viral proteins exposed during the fusion process. Interestingly, the researchers found that, in test tubes, antibodies taken from the blood of these mice were able to neutralize 23 out of 24 different HIV strains. The 24 strains comprised a representative panel of HIV virus samples from multiple international locations. This is a major advance because it constitutes the broadest immune response against HIV by a single immunogen that has been elicited to date. Investigators hypothesize that this broad effect may be elicited because some region in the fusion-competent immunogen is so fundamental to HIV function that it is conserved (does not mutate) across HIV strains.

Implications: A successful campaign to combat HIV/AIDS will depend on a vaccine's ability to neutralize a broad range of isolates of the virus. Although the findings from these experiments are preliminary, the demonstration that a single HIV immunogen can neutralize multiple HIV strains provides hope that the development of a broadly protective vaccine for HIV is possible.

LaCasse RA, Follis KE, Trahey M, Scarborough J D, Littman DR & Nunberg JH: Fusion-competent vaccines: Broad neutralization of primary isolates of HIV. Science 283: 357-362.

Peptide-Based AImmunization@ Holds Promise to Prevent or Treat Type l Diabetes

Background: Type 1 diabetes is caused when the immune system destroys the insulin-producing beta cells of the pancreas. Lack of insulin causes high blood sugar levels (hyperglycemia) and leads to kidney failure, blindness, nerve damage, and other serious complications. The onset of pancreatic inflammation, or insulitis, may be mediated by T lymphocytes that recognize beta cell proteins, such as glutamic acid decarboxylase (GAD). An inbred strain of mice called NOD (for non-obese diabetic) is unusually susceptible to spontaneous development of immuneBmediated diabetes. Now, researchers have shown that immunization of NOD mice with fragments of the GAD protein can prevent development of overt disease in pre-diabetic mice.

Advance: Investigators immunized NOD mice with certain fragments of peptides (chains of amino acids that serve as the building blocks of proteins) or mixtures of peptides from GAD. Each peptide or mixture tested prevented development of disease, if given before the appearance of insulitis. However, only one mixture of peptides reduced progression in mice with established insulitis. NOD animals that cannot develop a particular subset of T cells, called Th2 cells, were not protected by any of the peptides. While the mechanisms by which GAD peptides prevent disease are not understood, the research suggests that Th2 cells, and the cytokines they produce, are essential for the beneficial responses to peptide immunotherapy.

Implications: These findings suggest that it may some day be possible to immunize children to prevent the development or progression of type 1 diabetes. The ability to prevent or delay the onset of immune-mediated diabetes by childhood immunization would be a very important biomedical, scientific, and public health advance. Immunization would represent an enormously cost-effective, broadly applicable approach to modify autoimmune diseases like type 1 diabetes. While much remains to be learned before the knowledge gained in animal models can be translated into clinical practice, this study defines a very promising new avenue for translational researchBthe development of peptide-based "immunization" to prevent or treat type 1 diabetes and other autoimmune diseases.

Tisch R, Wang B & Serreze D: Induction of glutamic acid decarboxylase 65-specific Th2 cells and suppression of autoimmune diabetes at late stages of disease is epitope dependent. The Journal of Immunology 163(3): 1178-1187, 1999.

Vitamin A Reduces Mortality of African Children with AIDS

Background: Over 1 million children infected with the AIDS virus are estimated to be living in sub-Saharan Africa. Vitamin A deficiency is common in many developing countries, especially in children. Studies have shown that Vitamin A deficiency is particularly severe among AIDS virus infected people and that supplementing adult diets with vitamin A results in fewer deaths in some, but not all community-based trials. It was therefore thought that vitamin A supplementation might improve the long-term health prospects among children with AIDS in developing countries.

Advance: This study examined whether adding vitamin A to the diet could reduce the death rate among AIDS virus infected and uninfected children in Tanzania. The children in the study were age 6 months to 5 years old who had been hospitalized for pneumonia. The children received vitamin A or a placebo in the hospital and after they went home in addition to standard therapy for pneumonia. Vitamin A supplementation reduced the death rate due to all causes by two thirds among AIDS virus infected children and by half among uninfected children. For specific diseases that are the leading causes of death among children in this region, vitamin A supplements resulted in a two thirds reduction in AIDS-related deaths and a ninety percent reduction in diarrhea-related deaths.

Implications: Given the severity of the AIDS epidemic in developing countries especially the large number of children infected with the AIDS virus, there is an urgent need to find affordable ways to help reduce the impact of this disease. This study demonstrates that vitamin A supplementation can improve the health of AIDS virus infected and uninfected children as well. Vitamin A supplements are inexpensive and easy to distribute. Programs that provide vitamin A supplementation to communities where malnutrition is common could be useful in reduce the mortality from AIDS in children and benefit the health for all children participating.

Fawzi WW, Mbise RL, Hertzmark E, Fataki MR, Herrera MG, Ndossi G, and Spiegelman D: A radomized trial of vitamin A supplements in relation to mortality among human immunodeficiency virus-infected and uninfected children in Tanzania. Pediatric Infectious Disease Journal 18:127-33, 1999

Combination HIV Vaccine Induces Diverse Immune Responses in High HIV-Risk Population

Background: In broad terms, the human immune system provides two distinct forms of protective response. Humoral immunity is provided by antibodies that neutralize (eliminate) pathogenic invaders. Cell mediated immunity is provided by cytotoxic T cells (CTLs) that rid the body of infected and malignant cells. A vaccine capable of activating both of these immune system components may optimize immune response against HIV infections. Earlier studies showed that a combined approach is safe and can stimulate diverse immune responses in persons at low risk of HIV infection. The two vaccines tested in combination were SF-2 rgp120, which stimulates production of HIV neutralizing antibodies (to prevent HIV from infecting cells), and ALVAC-HIV vCP205, which stimulates cellular immunity provided by cytotoxic T cells (to kill HIV infected cells). Neither vaccine can cause HIV infection. SF-2 rgp120 is a genetically engineered copy of the HIV surface protein gp120. vCP205 consists of a weakened canarypox virus genetically altered to contain selected HIV genes.

Advance: The next step was to assess the combination vaccine in individuals at high risk of HIV infection. A group of volunteers at risk, due to drug use or sexual behavior, was enrolled in a randomized, double-blind clinical trial to study to determine the safety of, and the immune response generated by, the SF-2 rgp120/vCP205 vaccine combination. Study participants were placed in one of three groups. Group 1 received both vaccines, group 2 received one vaccine (vCP205) plus a placebo, and group 3 received two placebos. Investigators found that the SF-2 rgp120/vCP205 combination appears to be safe and can stimulate diverse immune response against HIV in high-risk individuals. Both vCP205 and the SF-2 rgp120/vCP205 combination induced anti-HIV immune responses in the majority of participants. More than half of those who received vCP205 alone, and more than 90 percent of those receiving the combination, developed antibodies that can inhibit HIV in a laboratory assayBhumoral immunity. Approximately one-third of participants who received either vCP205 alone, or the combination vaccine, developed anti-HIV CTL responsesBcell-mediated immunity. The combination vaccine appears to be safe and the associated adverse side effects are relatively mild.

Implications: This study was not designed to determine whether the vaccine combination can protect against HIV infection or AIDS development. In fact, during the course of the trial, 11 out of 436 participants became infected with HIV. (Infections are not surprising in a group of high-risk individuals.) However, the trial does provide strong evidence that the combination vaccine induces diverse immune responses in high-risk individuals. Before a large-scale efficacy trial is considered, more data on this vaccine strategy is needed. Additional NIH-sponsored studies, including evaluation of two newer canarypox HIV vaccines, are underway.

Belshe R, Stevens C, Gorse G, Buchbinder S, Sridhara R, Self S, Weinhold K, Sheppard H, Duliege AM, Meiger B, McNamara J & Flores J: Presentation at thirteenth meeting of the International Society for Sexually Transmitted Disease Research, Denver, Co., July 11-14, 1999.

Cancer Genetic Studies

Background: In 1994, as a result of the discovery of genes associated with colon cancer and in anticipation of the discovery of genes associated with breast and ovarian cancer, four NIH institutes funded studies to examine the ethical, legal and social issues surrounding genetic testing and counseling for heritable breast, ovarian and colon cancer risks. Eleven research projects were funded and, along with four other related research projects, form the Cancer Genetics Studies Consortium (CGSC). The consortium proved to be of great value; allowing researchers to collaborate in developing their research protocols, addressing issues surrounding informed consent and quality assurance of the DNA tests; and sharing information about what follow up care to offer to those found to test positive. The coordination fostered by the consortium has reduced duplication of effort and encouraged researchers to compare and challenge each other's findings on issues common among projects.

In September 1998, the NIH established the Cancer Genetics Network (CGN) to promote large-scale translational research. Among the goals of the CGN is to obtain answers to the next generation of outstanding issues in human cancer genetics such as and the elucidation of the role of cancer susceptibility genes in the onset and clinical course of cancer. The CGN, a network that includes eight U.S. medical research institutions specializing in the study of inherited predisposition to cancer, functions much like a cooperative clinical trials group to implement studies in clinical and genetic epidemiology. However, distinct from cooperative group efforts, a central registry of individuals at inherited risk of cancer is being developed to serve as an initial source of recruitment to the CGN studies.

Advance: Much has been learned over the past five years through CGSC projects. For example, different segments of the population have varied interest in genetic counseling and testing for inherited cancer risks. The Consortium has identified a number of factors which predict increased interest in genetic testing for colon cancer risk: increased age, increased education, strength of family history of colon cancer, Hawaiian ethnicity, increased perception of cancer risk, increased cancer worry, and an increase in perceived ability to cope with a positive test result. There is also evidence that some people consider undergoing genetic testing for altruistic reasons, such as a possible benefit to family members or to the research enterprise more broadly.

One study showed that there is more than one way to satisfactorily provide pretest education and counseling, but that education and counseling together were more likely to increase intentions of African American women to undergo testing. While the majority of women expressed an intention to be tested for breast and ovarian cancer risks, far fewer women were actually tested than would have been predicted. Another study demonstrated that family context was important in an individual's distress and ability to cope with positive test results. A third study showed that women with positive test results reported they would be more likely to do self-breast exam (92%), have clinical examinations (85%), and have mammography (69%). This last observation is crucial for further study if genetic testing for disease risk is to achieve the goal of increasing early screening and preventive behaviors.

Implications: In order for new genetic technologies to reduce cancer morbidity and mortality, screening, prevention, and management strategies to reduce risk must be proven to be beneficial. Further, individuals found to have mutations should adhere to follow up strategies demonstrated to reduce risk. The CGSC and CGN will play vital roles to enable researchers to examine issues surrounding genetic contributions to cancer susceptibility, adherence to prevention interventions and determination of factors that predict increased adherence, identification of strategies that enhance optimal outcome, and what impact these intervention strategies actually have on reducing morbidity and mortality. [secondary B diagnosis]

Vernon, S.W., D.J. Bowen and A.F. Patenaude (eds.) Psychosocial aspects of cancer genetic testing: findings from the cancer genetics studies consortium. Cancer Epidemiology, Biomarkers & Prevention Special Issue 8(4), 1998.

Bowen DJ, Farkas A, and Vernon SW: Psychosocial issues in cancer genetics: from the laboratory to the public. 326-328.

Glanz K, Grove J, Lerman C. et al: Correlates of intentions to obtain genetic counseling and colorectal cancer gene testing among at-risk relatives from three ethnic groups. 329-336.

Petersen GM, Larkin E, Codori AM, et al.: Attitudes toward colon cancer gene testing: survey of relatives of colon cancer patients. 337-344.

Codori AM, Petersen GM, Miglioretti DM, et al.: attitudes toward cancer gene testing: factors predicting test uptake. 345-351.

Vernon SW, Gritz ER, Peterson SK, et al.: Intention to learn results of genetic testing for hereditary colon cancer. 353-360.

Lerman C, Hughes C, Benkendorf JL, et al.: Racial differences in testing motivation and psychological distress following pretest education for BRCA1 gene testing. 361-367.

Durfy SJ, Bowen DJ, McTiernan A, et al. Attitudes and interest in genetic testing for breast and ovarian cancer susceptibility in diverse groups of women in western Washington. 369- 375.

Geller G, Doksum T, Bernhardt BA, and Metz SA. Participation in breast cancer susceptibility testing protocols: influence of recruitment source, altruism, and family involvement on women's decisions. 377-383.

Smith KR, West JA, Croyle RT, and Botkin JR. Familial context of genetic testing for cancer susceptibility: moderating effect of siblings' test results on psychological distress one to two weeks after BRCA1 mutation testing. 385-392.

Novel Antigen May Provide Basis for Vaccine Against Antibiotic Resistant Bacteria Involved in Hospital- and Community-Acquired Infections

Background: The bacterium *Staphylococcus aureus* is a major health concern as evidenced by the widespread occurrence of hospital- and community-acquired infections, including endocarditis, osteomyelitis, septic arthritis, pneumonia, and abscesses. Strains of *S. aureus* resistant to first-line drugs such as synthetic penicillins are becoming more common, especially in hospitalized patients. Of greatest concern, however, is the emergence of strains with reduced susceptibility to vancomycin, the antibiotic of last resort. Thus, there is a search for both alternative therapies and vaccines.

Investigators are exploring a number of vaccine targets based on molecules important in *S. aureus* replication. Bacteria have some molecules that are only produced when the bacteria replicate *in vivo* (in animals), but not *in vitro* (in the laboratory media in which they are often studied). Scientists have postulated that factors related to this differential expression must be critical for infection and disease progression, and therefore, may be important targets for vaccines to induce protective immunity.

Advance: Investigators determined that poly-N-succinyl B-1-6 glucosamine (PNSG), a surface sugar polymer isolated from *S. aureus*, is a major target for protective immunity. PNSG was already known to be an antigen of S. *epidermidis*, another species of *Staphylococcus.* However, PNSG had evaded discovery in studies of S. *aureus* due to PNSG's preferential expression *in vivo* during infection, but not *in vitro* during routine laboratory growth. Once discovered in *S. aureus*, PNSG was purified and injected into rabbits. The rabbits produced large amounts of PNSG antibodies, which persisted for at least 8 months. The researchers then injected the rabbit PNSG antibodies into mice and exposed the mice to eight different strains of *S. aureus*, including strains resistant to the antibiotic methicillin (a synthetic penicillin) and strains partially resistant to vancomycin. The majority of the mice receiving the rabbit PNSG antibodies were protected; most of the control animals died.

Implications: Because PNSG is relevant to two diverse *Staphylococcus* species, these findings raise the possibility that PNSG could be used as a vaccine not only to protect against *S. aureus*, but all significant staphylococcal diseasesBdiseases that are significant causes of hospital- and community-acquired infections in the U.S. Moreover, since *S. aureus* infections cause significant disease in farm animals, and therefore have substantial economic impact, this approach might be effective for veterinary vaccines as well. The potential usefulness of *in vivo* expressed antigens for other bacterial vaccines remains to be explored.

McKeeney D, Pouliot KL, Wang Y, Murthy V, Ulrich M, Döring G, Lee JC, Goldmann DA, & Pier GB: Broadly protective vaccine for *Staphylococcus aureus* based on an i*n vivo*-expressed antigen. Science 284:1523-1527, 1999

Natural Fatty Acids Might Play Key Role in Preventing Heart Attacks and Strokes

Background: Vascular inflammation is a key step in development of atherosclerosisBor Ahardening of the arteries@Bthat leads to many heart attacks and strokes. The series of events for atherosclerosis, as currently understood, is that: (1) the innermost layer of the artery, the endothelium, becomes damaged by cholesterol, environmental toxicants, oxidants, or infectious agents; (2) the damaged endothelial cells produce adhesion molecules; (3) the adhesion molecules allow white blood cells to accumulate in the vessel walls, causing inflammation and subsequent thickening of the artery so that it becomes vulnerable to complete blockage by a blood clot; and (4) if this blockage occurs, it can lead to the death of heart tissue (heart attack) or interruption of the blood supply to the brain (stroke). Intervening at any point in this cascade of events could, potentially, offer a way of reducing risks of heart disease and stroke from atherosclerosis.

Advance: NIH-supported scientists have shown that naturally occurring fatty acids can prevent vascular inflammation, a critical step in the development of atherosclerosis. Using both live mice and cultured human cells from the lining of the arteries, these scientists showed that fatty acid compounds called epoxyeicosatrienoic acids (EETs) and their metabolites suppressed the artery=s endothelium from producing adhesion molecules, thus reducing subsequent inflammation. The EETs appeared to act by inhibiting inflammatory precursors. These anti-inflammatory effects could be achieved by: (1) increasing the physiological concentration of EETs in endothelial cells *in vitro;* (2) transferring the human cytochrome P450 gene (CYP2J2) that produces the enzyme responsible for EET production into endothelial cells *in vitro*; and (3) intravascular administration of EETs *in vivo* in an established mouse model of vascular inflammation.

Implications: This work offers a new therapeutic approach for preventing atherosclerosis. The EETs or their stable analogs could be infused into blood vessels to reduce vascular inflammation and risk of heart attack and stroke in susceptible individuals. Alternatively, the human CYP2J2 gene could be transferred into arteries by gene therapy and help enhance production of EETs in the arterial walls, thus reducing vascular inflammation and atherosclerosis risk.

Node K, Huo Y, Ruan L-L, Yang B, Splecker M, Ley K, Zeldin DC, and Liao JK (1999) Anti-inflammatory actions of epoxygenase-derived eicosanoids. Science 285:1276-1279.

Blocking the Action of a Human Liver Carcinogen

Background: It has been estimated that as many as 90% of all human cancers have an environmental component to their cause. Hepatocellular carcinoma (HCC) is one of the leading causes of cancer death in the world. Each year HCC causes more than 200,000 deaths in the People-s Republic of China and is the leading cause of death in the city of Qidong, in the Jiangsu Providence. One common environmental factor in HCC is food contaminated with the fungus metabolite, aflatoxin. Aflatoxins are potent liver carcinogens which are consistent contaminants of the food supply in some parts of the world; the extent of contamination is dependent on local ecology and is not completely preventable. Aflatoxins are metabolized to an active compound that interacts with DNA to produce genetic alterations; when these alterations occur in critical oncogenes, they can lead to cancer.

Advance: This phase II chemoprevention trial used the anti-schistosomal drug, oltipraz, which is a potent inhibitor of aflatoxin-induced hepatocarcinogenesis in animal models. In this randomized, placebo-controlled double-blind study, two different drug regiments were used on human subjects from the Jiangsu Providence. Healthy individuals were either given a sugar pill (placebo), a weekly high dose or a daily low dose of oltipraz. Neither the individuals nor the health care providers knew the identity of the drugs until a code was broken. All the people enrolled in this study were studied for the production of aflatoxin metabolites in their urine. Daily administration of low doses of oltiprazled to an increase excretion of a harmless aflatoxin metabolite in the urine. Higher weekly administrations completely blocked the metabolism of aflatoxin to its harmful intermediates.

Implications: This study strongly suggests that administration of oltipraz would help reduce the risk of subsequent liver cancers in high risk populations exposed to aflatoxins, and represents an important chemoprevention regiment in the avoidance of an environmentally-induced cancer.

Wang JS, Shen X, He X, Zhu YR, Zhang BC, Wang JB, Qian GS, Kuang SY, Zarba A, Egner PA, Jacobson LP, Munoz A, Helzlsouer KJ, Groopman JD, Kensler TW: Protective alterations in phase 1 and 2 metabolism of aflatoxin B1 by oltipraz in residents of Qidong, People's Republic of China. J. Natl. Cancer Inst. 91:347-354, 1999

Chemoprevention of Tobacco Smoke-Induced Tumors

Background: Lung cancer kills more Americans than any other form of cancer. There is strong epidemiological data linking tobacco smoke with human lung cancer. However, tobacco smoke contains a large mixture of chemicals, and few suitable models exist which use tobacco smoke in laboratory animals in to study cause and effect. Thus identification of precise chemically-induced alterations in the cells of the lung and the development of possible chemoprevention strategies have been difficult. While certain chemopreventive strategies work against specific chemicals found in tobacco smoke, these protective agents were found to be ineffective against tobacco smoke-induced lung cancer in laboratory animals.

Advance: This team of researchers has developed a mouse lung cancer model which tests the effects of inhalation of cigarette smoke. Using this mouse model they have investigated the use of six different chemopreventive agents, including, two anti-oxidants (phenethylisothiocyanate, N-acetylylcysteine), green tea, *myo*-inositol, dexamethasone and the common drug, acetylsalicylic acid, aspirin. While several of these agents can prevent lung cancer induced by specific chemicals found in tobacco smoke, only a combination of *myo*-inositol and dexamethasone was found to significantly decrease the incidence and size of tobacco smoke-induced lung cancers.

Implications: Smoking cessation is the best prevention of lung cancer; however, due to the addictive nature of tobacco smoke, it is difficult for smokers to quit using tobacco products. Therefore chemoprevention strategies must be developed which could reduce the risk of lung cancer. These data, using an appropriate mouse model of lung cancer, clearly demonstrate an effective chemoprevention strategy using *myo*-inositol and dexamethasone.

Witschi H, Espiritu I, Uyeminami D: Chemoprevention of tobacco smoke-induced lung tumors in A/J strain mice with dietary myo-inositol and dexamethasone. Carcinogenesis 20:1375-1378, 1999.

SCIENCE CAPSULES

Alcohol and Adolescents: Capturing the Teachable Moment. By their senior year of high school, more than 80 percent of adolescents have consumed alcohol. A new study suggests that alcohol-using adolescents seen in emergency rooms subsequently experience fewer alcohol-related problems if they receive brief interventions by counselors at the time of their ER visit. Counselors in this study used emphathetic, reflective, nonconfrontational techniques, such as reviewing the circumstances that led to the ER visit and establishing goals that would prevent future incidents. [secondary B treatment]

Monti PM, et al: Brief Intervention for Harm Reduction with Alcohol-Positive Older Adolescents in a Hospital Emergency Department. Journal of Consulting and Clinical Psychology, in press.
(Statistics cited are from the Monitoring the Future Study, 1975-1998. Volume I: Secondary School Students. NIDA)

Knee Instability in Strength Training for Relief of Knee Osteoarthritis (OA). Exercise programs designed to improve muscle strength are known to provide modest increases in physical function for patients with OA. Recent studies, however, show that patients with the greatest amount of knee instability have the weakest relationship between muscle strength in their legs and physical functioning. This points to the necessity of research aimed at how to intervene at early stages and thereby reduce progression to physical dysfunction.

Sharma L, Hayes KW, Felson DT, Buchanan TS, Kirwan-Mellis G, Lou C, Pai Y-C, and Dunlop DD: Does laxity alter the relationship between strength and physical function in knee OA? Arth & Rheum 42: 25-32, 1999.

Grip Strength and Hand Osteoarthritis (OA). Investigators examining the association between the occurrence of hand OA and maximal grip strength found that women are two times more likely to have hand OA than men. However, grip strength was found to be an associated factor more for men with hand OA than for women. Because hand OA is common in older Americans, research on risk factors could have preventive implications.

Chaison CE, Zhang Y, Sharma L, Kannel W, and Felson DT: Grip strength and the risk of developing radiographic hand OA. Arth & Rheum 42: 33-38, 1999.

Survival Rates for Patients With Mycosis Fungoides. Mycosis fungoides is a type of lymphoma, a cancer of the immune system, for which there is no cure but for which there are many treatments that offer long remissions. A population-based assessment of survival trends in 1633 U.S. patients revealed the following: approximately 66 percent of cases survived 11 years; once the 11th year was reached, there was little additional mortality attributed to mycosis fungoides; prognosis for the cohort improved substantially during the 20-year period of study; and black race and advanced age were associated with poorer survival. Data on age, gender, and ethnicity can provide useful information for detecting more cases at a treatable stage.

Weinstock MA and Reynes JF: The changing survival of patients with mycosis fungoides, a population-based assessment of trends in the United States. Cancer 5: 208-12, 1999.

Cerebral Palsy Associated with Inflammatory and Immune Responses. Cerebral palsy causes life-long disability for more than 750,000 Americans. Long thought to be due to insufficient oxygen supply during the birth process, cerebral palsy has not declined with advances in obstetrical and newborn care. New findings show that blood from newborns later diagnosed with cerebral palsy contains higher than normal concentrations of chemical signals by which active immune cells communicate. Newborns who later exhibited CP also had markers of blood clotting abnormalities that predispose older children to strokes. Thus, the immune system, whether reacting to infection before birth or by autoimmune reactions, may play a previously unrecognized role in causing cerebral palsy. This discovery may open new approaches to preventing cerebral palsy by focusing on the potential role of immune function in causing this disorder.

Nelson KB, Dambrosia JM, Grethher JK, and Philips TM: Neonatal cytokines and coagulation factors in children with cerebral palsy. Ann Neurol. 44: 665-75, 1998.

Grethher JK, Dambrosia JM, Nelson KB, and Philips TM: Interferons and cerebral palsy. J. Pediatrics 134: 324-43, 1999.

Benefits of Low-dose Aspirin for Stroke Prevention. The two carotid arteries in the neck carry blood from the heart to the brain, and a stroke can occur when a carotid artery becomes blocked as a result of the buildup of fatty deposits. Surgery to remove these deposits, known as carotid endarterectomy (CE), has been proven to be beneficial in carefully defined patients at centers that have a low risk for surgical complications, and a great deal of research has established that aspirin reduces the risk of stroke in certain patients. A recent study has now answered the dose question for patients who will receive carotid endarterectomy surgery, showing that lower doses of aspirin (81 or 325mg daily) on a pre- and post-surgery schedule work better than higher doses (650 or 1300mg) to prevent strokes. This is good news because lower doses of aspirin are easier to take and better tolerated, so more people can get the full benefit of aspirin to prevent strokes following CE. According to the most recent statistics available from the National Center for Health Statistics, the number of CE procedures done at non-Veterans hospitals in the United States rose from 60,000 in 1991, to 130,000 in 1995. [secondary B treatment]

Taylor WD, Barnett HJM, Haynes BR, Ferguson GG, Sackett DL, Thorpe KE, Simard D, Silver FL, Hachinski V, Clagett GP, Barnes R, and Spence JD: for the ASA and Carotid Endarterectomy (ACE) Trial Collaborators. A randomized trial of low and high dose aspirin for patients undergoing carotid endarterectomy. The Lancet 353(9171): 2179-2184, 1999.

The Prevention of Infection (Cytomegalovirus) After Kidney Transplantation. Cytomegalovirus disease is a major complication of organ transplantation. This study shows that

prophylactic treatment with valacyclovir is a safe and effective way to prevent CMV disease after renal transplantation. [secondary B treatment]

Lowance D, et al., *Valacyclovir for the Prevention of Cytomegalovirus Disease after Renal Transplantation* New England Journal of Medicine 1999; 340: 1462-1470.

Oxygen May Limit Damage in Retinal Detachment. Retinal detachment is a condition in which the sensory retina separates from its normal position lining the back of the eye near the capillary bed which is the primary source of nutrients and oxygen. Scientists have recently found that animals with induced detached retinas demonstrated less retinal cell death and greater cell integrity when maintained in a high oxygen environment for several days. Since oxygen treatment can be easily administered in physicians' offices and hospitals, further research in this area may lead to a new approach to delaying the progression of cell damage in retinal detachment in humans.

Mervin K, Valter K, Maslim J, Lewis G, Fisher S, and Stone S: Limiting photoreceptor death and deconstruction during experimental retinal detachment: the value of oxygen supplementation. Am J Ophthalmol 128(2):155-164, 1999.

Noise-Induced Hearing Loss: Both Common and Preventable. Hearing scientists and clinicians have long been aware that exposure to toxic levels of noise can result in hearing loss. NIH-supported scientists are examining the molecular pathway that leads to noise-induced hearing loss, the genetic factors that predispose individuals to noise damage, and various options for preventing hearing loss associated with noise exposure. A public awareness campaign, WISE EARS!, has launched to inform the American public about the progressive damage to hearing that accompanies exposure to toxic noise.

Otitis Media. Otitis media, or middle ear infection, is the most common reason that a sick child is brought to the attention of a physician, at an estimated cost of 4-5 billion dollars a year in the United States. With the emergence of antibiotic resistant bacterial pathogens, it is essential that the pathogenesis of otitis media be understood, and that vaccines be developed to prevent this disorder. A Phase One Clinical Trial of a promising vaccine candidate, shown in pre-clinical studies to be effective in preventing otitis media in animal models, is currently underway in the NIH Clinical Center.

Gu X-X et al: Detoxified lipooligosaccharide from nontypeable *Haemophilus influenzae* conjugated to proteins confers protection against otitis media in chinchillas. Infection and Immunity 65(11): 4488-4493, 1997.

Breast-feeding and Disease Prevention. A study conducted in a rural Egyptian population has found that infants who consumed breast milk consistently beginning immediately after birth had a marked reduction in diarrhea throughout the first six months of life. The reduction of infantile diarrhea is possibly due to the presence of colostrum found in breast milk during the first few

days after delivery. Early initiation of breast-feeding in infants in developing countries may reduce the burden of diarrheal episodes.

Clemens J, Abu-Elyazeed R, Rao M, Savarino S, Morsy BZ, Kim Y, Wierzba T, Naficy A, and Lee YJ: Early initiation of breastfeeding and the risk of infant diarrhea in rural Egypt. Pediatrics 104: 1-5, 1999.

Preventing Diarrhea Caused by Rotarvirus. In a related study conducted jointly by NIH, the Centers for Disease Control and Prevention, and the U.S. Navy, researchers determined that improving sanitation and other living conditions does not appear to protect against rotavirus. Rotavirus is the most common cause of severe diarrheal disease in the world, and, if untreated, can lead to dehydration and death. Unlike many other diarrheal diseases that can be reduced through steps such as improved sanitation and reduction of household crowding, the researchers did not find any benefit to such traditional remedies. While breast-feeding during the first year of life was found to protect infants from the disease, the only comprehensive measure for preventing rotavirus infection on a large scale is vaccination. The researchers concluded that routine administration of a rotavirus vaccine should be a priority in countries where the disease is a public health problem.

Naficy AB, Abu-Elyazeed R, Holmes JL, Rao MR, Savarino SJ, Kim Y, Wierzba TF, Peruski L, Lee YJ, Gentsch JR, Glass RI, and Clemens JD: Epidemiology of rotavirus diarrhea in Egyptian children and implications for disease control. Am J Epidemiol; In press.

High HIV RNA Levels Major Risk Factor for Mother-to-Child HIV Transmission. The amount of the AIDS virus HIV in a pregnant woman=s blood, known as viral load, is the prime risk factor for transmitting the virus from mother to child, although several factors can contribute to HIV transmission. The results of this research suggest that reducing HIV viral loads in a woman=s blood during pregnancy is an additional way to continue to reduce the transmission of HIV from mother to child.

Mofenson LM, Lambert JS, Stiehm ER, Bethel J, Meyer III WA, Whitehouse J, Moye Jr J, Reichelderfer P, Harris, DR, Fowler MG, Mathieson BJ, and Nemo GJ: Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. NEJM 341: 385-393, 1999.

Healthy Habits Are Hard To Shake. Based on a follow-up of the cohort that participated in the Child and Adolescent Trial of Cardiovascular Health (CATCH), it appears that programs to promote healthy diets and regular physical activity in children maintain an effect long after the programs themselves have terminated. Although the advantages among the intervention group as compared with the control group were not as pronounced 3 years after the trial as at the conclusion of the trial, children who participated in the intervention group showed lower levels of energy intake from saturated fats, higher levels of vigorous physical activity, and greater knowledge about healthful dietary habits than the control group.

Nader PR, Stone EJ, Lytle LA et al: three-year maintenance of improved diet and physical activity: the CATCH Cohort. Arch. Pediatr. Adolesc. Med. 153:695-704, 1999.

Lower Blood Pressures Mean Smaller Hearts. Left ventricular hypertrophy, or enlargement of the left ventricle, the chamber of the heart responsible for pumping freshly oxygenated blood throughout the body, is known to be a substantial risk factor for cardiovascular disease and represents heart damage caused by high blood pressure. Data derived from the world-renowned Framingham Heart Study provide strong grounds for believing that the great progress made in preventing, detecting, and controlling high blood pressure between 1950 and 1980 has translated into similar dramatic progress in limiting associated heart damage.

Mosterd A, D'Agostino RB, Silbershatz H et al: Trends in the Prevalence of hypertension, antihypertensive therapy, and left ventricular hypertrophy from 1950 to 1989. NEJM 340:1221-1227, 1999.

HIV-1 viral load differences in men and women may call for earlier treatment for women. The quantity of HIV virus in the blood (viral load) is important in predicting progression to AIDS and in determining initiation of therapy for HIV. While men and women progress to AIDS at the same rate, researchers have found that women have lower viral load than men do at the same stage of disease. Although the biological mechanism is not known, current therapy recommendations may need to be changed for women infected with HIV in order for them to receive the full benefit of treatment.

Farzadegan H, Hoover DR, Astemborski J, Lyles CM, Margolick JB, Markham RB, Quinn TC, and Vlahov D. Sex Differences in HIV-1 viral load and progression to AIDS. The Lancet 352: 1510-1514.

Curtailing Smoking in Minority Girls. Smoking among African-American and Hispanic adolescents increased in the 1990s despite a concurrent decrease among other groups. Minority girls who received a 15-session school-based intervention in the 7th grade that teaches social resistance skills and promotes personal and social competence showed reduced smoking initiation among non-smokers and reduction in the rate of smoking escalation among minority girls. These results demonstrate that a school based prevention program that has previously been found to be effective among white adolescents is also effective among urban, minority girls.

Des Jarlais DC, Perlis T, Friedman SR, Deren S., et al. "Declining Seroprevalence in a Very Large HIV Epidemic: Injecting Drug Users in New York City, 1991 to 1996." Am J Public Health 88(12): 1801-1806, 1998.

Effects of Community Policies to Reduce Youth Access to Tobacco. In a 32-month study in 14 Minnesota communities, seven "intervention communities" passed a comprehensive youth access ordinance ensuring merchant compliance with tobacco age-of-sale laws such as licensing fees, vendor penalties, clerk penalties, vending machine bans, self-service bans, purchaser penalties, and compliance checks. At the end of the study, in all seven intervention sites, daily smoking by youth in grades 8, 9, and 10 was reduced significantly compared to those youth in the

seven "control" communities that did not organize to change ordinances, policies, and practices. This study provides evidence that community policies to reduce youth access to tobacco can have a significant effect on youth smoking rates.

Forster JL, Murray DM, Wolfson M, et al.: The effects of community policies to reduce youth access to tobacco. American Journal of Public Health 88: 1193-1198, 1998.

Treatment for Ductal Carcinoma In Situ. A recent trial sponsored by the NIH-supported National Surgical Adjuvant Breast and Bowel Project (NSABP) demonstrated that the addition of tamoxifen to lumpectomy and radiotherapy in women with ductal carcinoma in situ (DCIS) reduces the risk of both cancer recurrence in the same breast and later cancer in the other breast. Taken together with earlier results, the findings suggest that lumpectomy, breast irradiation and tamoxifen can substitute safely for mastectomy in the treatment of DCIS.

Fisher B, Dignam J, Wolmark N, et al.: Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial. Lancet 353: 1993-2000, 1999.

Wilcken NR.: Tamoxifen hits the target in situ. Lancet 353: 1986-1987, 1999.

Efficacy of Exercise as an Aid for Smoking Cessation in Women. Researchers studied whether sedentary female smokers in a behavioral smoking cessation program would benefit from vigorous exercise. The women in the study participated in a 12-session, group-based smoking cessation program; approximately half of the women also attended 3 weekly supervised exercise sessions for 12 weeks. At the end of 12 weeks, significantly more women in the smoking cessation and exercise program remained abstinent from smoking as compared to women in the behavioral smoking cessation program without exercise (16.4 percent vs. 8.2 percent), and differences in the "success rate" of the program held throughout the first year.

Marcus BH, Albrecht AE, King TS, et al.: The efficacy of exercise as an aid to smoking cessation in women. Archives of Internal Medicine 159: 1229-1234, 1999.

Reducing HIV-Risk for African American Adolescents Through Abstinence and Safer Sex. An NIH-funded evaluation of risk-reduction interventions promoting sexual abstinence and safe sex found both to reduce HIV sexual risk behaviors among Black youth. For sexually experienced teens, the emphasis on safer-sex was shown to be particularly effective and to have longer-lasting effects.

Jemmott JB 3rd, Jemmott LS, Fong GT: Abstinence and safer sex HIV risk-reduction interventions for African American adolescents: A randomized controlled trial. Journal of the American Medical Association 279: 1529-1536, 1998.

Impediments to Medication Adherence Among HIV-infected Adults. Although currently available medication regimens for HIV infection can be quite effective, many individuals are discouraged by the frequency and conditions associated with taking needed drugsBfor example, only with meals or during normal sleeping hoursBand by changes in their daily routines. NIH researchers have conducted focus groups with HIV-infected patients to determine what strategies facilitate, or prevent, successful adherence and to investigate how the relationship between a health care provider and patient may influence adherence. Three strategies were found to be used most often to aid adherence: carrying special containers for variety of medications needed in the course of a day; patient and, if necessary, repeated explanations of medication requirements by the health care provider; and carrying food and water that may be called for when taking certain medications. [secondary B treatment]

Murphy, DA, Roberts, KJ, Martin, DJ, Marelich, W, & Hoffman, D. Barriers to antiretroviral adherence among HIV-infected adults. AIDS Patient Care and STDs, in press, 1999.

Evaluating Approaches to Reducing Risk for HIV Infection in People with Serious Mental Illness. Because many severely mentally ill adults frequently engage in high-risk behavior practices, HIV-infection is found alarmingly often among such persons. In an evaluation of risk-reduction strategies, participants who were randomly assigned to attend a 7-session small-group cognitive-behavioral HIV risk-reduction intervention were more likely than their counter-parts, who received a time-matched comparison intervention, to increase condom use and to have more positive attitudes toward condoms, with women particularly responsive to the intervention. Many of the behavior-change effects were present at 3-, 6- and 9-month follow-up assessments, but most diminished by the 12-month follow-up, underscoring the need for tailored and ongoing HIV prevention efforts integrated into community programs that serve people with serious mental illness.

Otto-Salaj LL, Kelly JA, Stevenson LY, Hoffmann R, Kalichman, SC: Outcomes of a randomized small-group HIV prevention intervention trial for people with serious mental illness. In press.

Traumatic Stress Associated with a Diagnosis of Metastatic Breast Cancer May Be Relieved by Mental Health Care. Much like individuals who have survived multiple shootings and motor vehicle accidents, up to one-half of women diagnosed with metastatic breast cancer may experience clinically significant levels of post-traumatic stress symptoms, including, for example, intense fear or a sense of helplessness or disorganized or agitated behavior. In a baseline study of women with metastatic breast cancer conducted before the start of a psychotherapeutic intervention, NIH researchers determined that women reporting the most past stressful life events and poorest social supports for their illness tended to experience the most severe intrusive, repetitive thoughts of their illness. Those women with very limited social networks were most likely to avoid thinking about their diagnosis altogether, a severe symptom of trauma. These findings suggest that inadequate and aversive social environments may critically exacerbate the effects of the cancer on women=s adjustment to their illness and may affect their treatment and recovery. [secondary B treatment]

Butler LD, Koopman C, Classen C, Spiegel, D: Traumatic stress, life events, and emotional support in women with metastatic breast cancer: Cancer-related traumatic stress symptoms associated with past and current stressors. Health Psychology In press, 1999.

Major Depression Reduces the Quality of Life for Patients with Coronary Artery Disease. NIH-researchers recently demonstrated that people aged 65-and-older who have coronary artery disease and also suffer from major depression are twice as likely as their non-depressed counterparts with heart ailments to report problems in basic activities of daily living, such as the ability to eat, dress, groom, and bathe oneself, to use the toilet, and to walk. Deficits in any of these areas of function may affect the individual=s quality of life and are likely to have a major influence on the frequency with which they seek health care and, in turn, on the cost of their illness. The question now is whether treating or even attempting to prevent major depression among those with heart disease will reduce disabling emotional symptoms and enhance abilities to engage in activities of daily living. [secondary B treatment]

Steffens DC, O=Connor CM, Jiang WJ, Pieper CF, Kuchibhatla MN, Arias RM, Look A, Davenport C, Gonzalez MB, Krishnan KRR: The effect of major depression on functional status in patients with coronary artery disease. Journal of the American Geriatric Society 47:319-322, 1999

It=s 9:00 P.M. Have You Tucked Your Teen In? The steady shift toward early morning school openings can have substantial consequences, including diminished academic performance, memory lapses, and mood changes, as well as behavior problems. NIH research has shown that in susceptible young people, this pattern may lead to academic, behavioral, and psychological problems, as well as increased risk for accidents and injuries, particularly for teens who drive. Previous research has indicated that optimal alertness in adolescents requires over 9 hours of sleep nightly. This study shows that early school start times for adolescents are associated with significant sleep deprivation, both because 9 hours of sleep would require unrealisticBif not unattainableBbedtimes and because many younger teens, in particular, may have a greater biological need for sleep.

Carskadon MA, Wolfson AR, Acebo D, Tzischinsky O, Seifer, R: Adolescent sleep patterns, circadian timing, and sleepiness at a transition to early school days. Sleep, 21: 871-881, 1998.

Reducing HIV Risk Among Women. A recent randomized clinical trial evaluated an HIV risk-reduction intervention based on the Information-Motivation-Behavior model. Post-intervention and follow-up data indicated that women who participated in the experimental intervention, more so than a matched control group, enhanced their knowledge about how to reduce risk and strengthened intentions to reduce their risk for HIV-infection. Benefits of the active intervention included increased condom use, more discussion with partners about condom use and HIV testing, and a greater likelihood to refuse unprotected sex.

Carey MP, Braaten LS, Maisto SA, Gleason JR, Forsyth AD, Durant IE, Jaworski BC. Using information, motivational enhancement, and skills training to reduce the risk of HIV infection for low-income urban women: A second randomized clinical trial. Health Psychology, in press, 1999.

Encouraging International Research on AIDS Risk Reduction. NIH-funded researchers have found that a worksite-based AIDS prevention program for port workers in Santos, Brazil, led to both a decrease in sexual interactions outside of one=s primary relationship and an increase in condom use. These marked behavior changes were accomplished, moreover, at modest cost.

Hearst N, Lacerda R, Gravata N, Hudes E, Stall R. Reducing AIDS risk among port workers in Santos, Brazil. American Journal of Public Health 89: 76-79, 1999.

Recurrence of Episodes of Major Depression. A long-term follow-up study of psychiatric patients who sought treatment for an episode of major depression found that over a 15-year period, 80% of these patients experienced at least one additional episode of major depression. Even among patients who recovered for a period of at least 5 years, 60% suffered another depressive episode within the next 10 years. The significant predictors of recurrence of depression included being female, the number and duration of prior episodes of depression, and not being married. This study provides useful information for predicting who will or will not experience a recurrence of depression after their first major depressive episode and, thus, how the amount and duration of antidepressant medications should be adjusted for them by mental health providers. [secondary B treatment]

Mueller TI, Leon AC, Kellen DA, Endicott J, CoryellW, Warshaw M, Maser, JD: Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. American Journal of Psychiatry, 156: 1000-1006, 1999.

Social and Productive Activities Confer Survival Advantages to the Elderly. When previous studies found that older people who remained active lived longer, scientists assumed that the survival advantage resulted from improved cardiopulmonary fitness attributable to physical activity. A new study suggests that social activities (church attendance, travel, etc.) and productive activities (gardening, community work, etc.) involving little or no enhancement of fitness lowered the risk of all-cause mortality over a thirteen-year period just as much as fitness activities (e.g., swimming, and walking). This study suggests that a wider range of mechanisms, both psychological and psychosocial, may be involved in the association between activity and mortality than had been previously thought.

Glass TA, Mendes de Leon C, Marottoli R, and Berkman LF: Population based study of social and productive activities as predictors of survival among elderly Americans. British Medical Journal 319: 478-83, 1999.

Differences in Blood Pressure and Cholesterol Responses to Exercise in Older Men are Related to Genetic Variation. Exercise improves cardiovascular disease risk factors, such as

blood pressure and cholesterol, but the size of these effects varies widely among persons. A recent study in older men with high blood pressure suggests that this variation in responses is affected by at least three genes: one for a protein that regulates blood pressure changes (angiotensin-converting enzyme, ACE), one for a cholesterol-carrying protein (apolipoprotein E, apoE), and one for an enzyme regulating cholesterol levels (lipoprotein lipase, LPL). There are different variants of these genes (genotypes) in the population. When the men were grouped according to their genotypes, the groups differed significantly in the degree of exercise-induced changes in blood pressure and cholesterol. These results suggest that determining these genotypes may help identify which persons are likely or unlikely to improve blood pressure and cholesterol significantly with exercise training.

Hagberg JM, Ferrell RE, Dengel DR, and Wilund KR: Exercise training-induced blood pressure and plasma lipid improvements in hypertensives may be genotype dependent. Hypertension 34: 18-23, 1999.

High Levels of Estrogen and Testosterone in Women are Associated with Risk of Breast Cancer. One in eight women in the U.S. will develop breast cancer, and deaths from breast cancer account for 17% of all cancer deaths in women in the U.S. Endogenous (naturally circulating) levels of estrogen may play an important role in the development of breast cancer. There has also been increasing interest in the relationship of testosterone to risk of breast cancer in women. Scientists examining a large group of postmenopausal women found that higher levels of both endogenous estrogen and testosterone are significantly associated with increased risk of breast cancer. This indicates that measuring these hormones may be useful in estimating a woman's risk for breast cancer. The findings suggest potential benefits for antiestrogen treatment for primary prevention in those at risk.

Cauley JA, Lucas FL, Kuller LH, Stone K, Browner W, and Cummings SR: Elevated serum estradiol and testosterone concentrations are associated with a high risk for breast cancer. Annals of Internal Medicine 130:270-7, 1999.

HIV Risk Behaviors Can Be Predicted from the Five-Factor Model of Personality. The AIDS epidemic provides a clear challenge to understand health risk behaviors and to design programs to change them. The Five-Factor Model of personality seeks to understand behavior in terms of personality traits that remain fairly constant over time, such as neuroticism and consientiousness. An analysis of HIV risk perceptions and behaviors in a high-risk, disadvantaged, rural and minority population showed that these personality traits can contribute to the understanding of problem behaviors. High Neuroticism and low Conscientiousness were associated with risky behavior; low Conscientiousness further predicted failure to benefit from a four session intervention program; and low Openness to Experience was associated with the denial of the risk of infection. These findings suggest that personality traits are related to health risk variables, and that systematic investigation of personality links to problem behaviors may be a useful first step to formulating theories of behavior change and designing appropriate interventions to reduce high risk behaviors.

Trobst KK, Costa PT Jr, Wiggins JS, Herbst JH, Masters HL III, and McCrae RR: Problem behavior and the five-factor model: HIV infection risks, perceived vulnerability, and precautionary behavior. Special Issue: Personality Perspectives on Problem Behavior. Journal of Personality, in press, 1999.

Genetics of Breast Cancer. Mutant BRCA1 or BRCA2 genes can increase a woman's risk of developing breast cancer, but the frequency of these mutations in certain populations is unknown. By evaluating 268 breast cancer patients of Ashkenazi Jewish descent, researchers at the Mount Sinai School of Medicine found that about 18 percent had specific BRCA1 or BRCA2 mutations, and that two specific BRCA1 mutations were associated with a 36 percent lifetime risk for breast cancer, which is three times the risk for the general U.S. population. Although larger studies are needed to clarify the relationships between genes and breast cancer risk, genetic screening may eventually enhance presymptomatic decision-making by at-risk patients, who may opt for early interventions such as "watchful waiting," prophylactic mastectomy, or hormone prophylaxis.

Fodor FH, Weston A, Bleiweiss IJ, McCurdy LD, Walsh MM, Tartter PI, et al.: Frequency and carrier risk associated with common BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer patients. American Journal of Human Genetics 63:45-51, 1998.

Low Vitamin D Levels and Bone Fractures in Women. The risk of hip fractures increases exponentially with age, but some of these injuries may be prevented with adequate vitamin D intake, according to a study conducted at the Brigham and Women's Hospital in Boston. By evaluating 166 postmenopausal women admitted to the hospital for hip or joint replacement surgery, the investigators found that postmenopausal women who presented with hip fracture also showed signs of vitamin D deficiency. Because vitamin D deficiency is preventable through proper nutrition and vitamin supplements, physicians and older patients should be made aware of the importance of vitamin D to healthy bones.

Leboff MS, Kohlmeier L, Hurwitz S, Franklin J, Wright J, and Glowacki J. Occult vitamin D deficiency in postmenopausal US women with acute hip fracture. JAMA 281:1505-1511, 1999.

Male Circumcision Lowers the Risk of AIDS Infection. Previous evidence suggests that male circumcision might reduce the risk of sexually transmitted diseases in adulthood. This evidence was recently expanded in a study in Uganda that showed circumcision before the age of 12 reduced the risk of AIDS virus infection in men. The study also revealed that circumcision after age 20 did not protect against the AIDS virus infection and, therefore, should not be considered as a preventive public health measure.

Kelly R, Kiwanuka N, Wawer MJ, Serwadda D, Sewankambo NK, Wabwire-Mangen F, Li C, Konde-Lule JK, Lutalo T, Makumbi F, and Gray RH: Age of male circumcision and risk of prevalent HIV infection in rural Uganda. AIDS 13: 399-405, 1999.

Impact of Vitamin A on AIDS. In certain developing countries, a correlation was observed between low levels of vitamin A in mothers due to malnutrition and increased transmission of the AIDS virus to their newborn children. A new study designed to directly test this linkage failed to demonstrate any significant reduction of mother-to-child transmission of the AIDS virus when supplements of vitamin A and other micronutrients were given to infected pregnant women. However, Vitamin A and micronutrient dietary supplementation generally improved the health status of both HIV-infected mothers and their children. These results indicate that although Vitamin A will not affect mother-to-child transmission of AIDS, the supplements can decrease morbidity in both mothers and children with the disease.

Fawzi WW, Msamanga GI, Spiegelman D, et al. Randomized trial of effects of vitamin supplements on pregnancy outcomes and T cell counts in HIV-1 infected women in Tanzania. The Lancet 351: 1477-1482, 1998.

Presence of Other Sexually Transmitted Diseases Increases AIDS Virus Transmission. Previous studies suggest that the presence of sexually transmitted diseases (STDs) increases a woman=s risk of acquiring AIDS. The precise means by which this occurs has not been well-defined until recently. A new study from Kenya indicates that a specific immune factor, IL-10, generated in response to other sexually transmitted diseases is found in the genital tract and appears to enhance vulnerability to HIV infection. This study clarifies our understanding of how infection with non-ulcer forming STDs increases the risk of acquiring AIDS.

Cohen CR, Plummer FA, Mugo N, Maclean I, Shen C, Bukusi EA, Irungu E, Sinei S, Bwayo J, and Brunham RC: Increased interleukin-10 in the endocervical secretions of women with non-ulcerative sexually transmitted diseases: a mechanism for enhanced HIV-1 transmission? AIDS 13: 327-332, 1999.

A Genetic Factor Associated with Premature Delivery. Complications resulting from premature births account for the majority of newborn deaths in developed countries. Recent data suggests that the body=s immune response to low level genital infections may be a risk factor for premature birth. This study identified a rare genetic change in the gene encoding a component of the immune response, tumor necrosis factor (TNF) that correlates with the pre-term rupture of the membrane surrounding the fetus leading to premature delivery. Based on these results, a genetic test may be developed to diagnose the predisposition to premature birth and the possibility of TN- related preventative therapy.

Roberts AK, Monzon-Bordonaba F, Van Deerlin PG, Holder J, Macones GA, Morgan MA, Strauss JF and Parry S. Association of polymorphism within the promoter of the tumor necrosis factor alpha gene with increased risk of preterm premature rupture of the fetal membranes. American Journal of Obstetrics and Gynecology 180: 1297-1302, 1999.

STD Treatment and AIDS Virus Transmission. Infection with sexually transmittted diseases (STDs) is known to enhance the risk of acquiring AIDS. Two recent studies tested whether controlling (STDs) would lower the incidence of AIDS virus infection for populations at risk. The first study conducted in a Tanzanian community with a low initial level of AIDS virus

infection, found that curing adults with symptomatic STD, prevented 40% of potential new AIDS virus infections. In the second study in a Ugandan population with a high level of long established AIDS virus infection, even mass treatments of persons infected with STDs do not result in a decrease in the expected incidence of the AIDS virus infection. These two studies strongly suggest that treatment of STDs before the spread of AIDS within a population can prevent the enhanced transmission of the AIDS virus infection. Further studies will clarify how the population dynamics of these two diseases interact to produce this situation.

Wawer AJ, Sewankambo NK, Serwadda D, Quinn TC, Paxton LA, Kiwanuka N, Wabwire-Mangen F, Li C, Latalo T, Nalugoda F, Gaydos CA, Moulton LH, Meehan MO, Ahmed S, the Rakai Project Study Group and Gray RH: Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomized community trial. The Lancet 353: 525-535, 1999.

Hitchcock P and Fransen L: Commentary: Preventing HIV infection: lessons from Mwanza and Rakai. The Lancet 353: 513-515, 1999.

Intervention Programs Reduce Asthma Severity. Asthma is more prevalent among children in urban areas with high levels of poverty and large minority populations. The National Inner City Asthma Study evaluated a model intervention program to work with asthmatic children and their families. Intervention involving individualized counseling on reduction of exposure to asthma causing agents in the home environment resulted in reduced asthma symptoms, less frequent asthma-related hospital visits, as well as two additional asthma-free weeks per child. This study shows that an individually tailored, multifaceted intervention model that utilizes a social worker trained in asthma management can reduce asthma symptoms in inner-city children.

Evans, R. et al (in press). Intervention of asthma counselors reduces asthma severity among inner-city children. Journal of Pediatrics in press.

STORIES OF DISCOVERY

The Fight against Influenza Receives a Shot in the Arm

The body has an arsenal of defenses that it uses to ward off foreign invaders such as parasites, bacteria, fungi, and viruses. To protect the body, these defenses must recognize special markers on the foreign microbes called antigens. Once the antigens are recognized, the body produces protective molecules called antibodies that eliminate the invader. Vaccines that contain a weakened or killed bacteria or virus, or even just parts of the microbe, give the body a head start in this fight. The body becomes primed for the microbe and if the invader enters the body, the primed immune system is able to quickly eliminate it before it can cause an infection. Pathogens may also be inactivated for use as vaccines by inserting mutations into their genetic material (genomes). The technique of inserting mutations into viral genomes and then producing virus particles is part of a process known as reverse genetics. A team of investigators supported by the NIH at the University of Wisconsin-Madison (UW) has developed a new approach to reverse genetics. They have created, for the first time, live, replicating influenza A virus starting with individual DNA building blocks. Influenza A virus was the mysterious organism that caused the 1918 Spanish influenza pandemic and led to more than 20 million deaths worldwide. This research has far ranging implications for prevention of flu and of other infectious diseases, for gene therapy, and for understanding the ways flu strains mutate, spread, and cause widespread morbidity and mortality.

Influenza vaccine development has been hindered by the complexity of the virus' genetic makeup, its multi-segmented genome, and the previously inefficient methods of producing vaccine-suitable viruses in the laboratory. Moreover, these hindering factors compound one another. Influenza viruses contain a genome of eight different segments of viral RNA (rather than DNA) and RNA-dependent viral enzymes. For the virus to reproduce (generate new viral particles), it must fabricate virus proteins. To generate these proteins, the viral RNA must first be copied into its complement (messenger RNA) using RNA-dependent viral enzymes. Without these enzymes, the viral RNA would be processed improperly and would not produce any viral proteins or viral particles. Making the situation particularly vexing for researchers is the fact that all eight of the RNA segments of the flu virus must be inserted into the same cell in order to produce new viral particles. Furthermore, adding "helper strains" of intact flu virus had previously been required to yield viable, replicating virus.

These hurdles now have been largely overcome. The UW group, led by Yoshiro Kawaoka, introduced eight plasmids (independent segments of DNA capable of replicating)Bone for each segment of influenza RNABinto a dish of about one million living kidney cells. They also introduced nine other plasmids into the cells that serve as building blocks for the proteins needed to make a complete influenza virus. The plasmids invade the cells in random combinations and, if the right combination is achieved, they can form an infectious flu virus. To prove that the new virus was active, the researchers allowed a new generation of influenza A virus to be created, and then used it to infect a separate batch of cells. A genetic analysis of the virus in the newly infected cells showed that it was an exact replica of the original virus.

In terms of efficiency, the new system is a 1,000-fold improvement over current methods. Moreover, the UW system produces a more useful product. While the previous process did generate altered viruses, very few of them would have the desired genetic trait. The new system gives scientists full access to every nucleotide in the virus genome.

This significant development in reverse genetics was built on a solid foundation of research in the 1980s and 1990sBmuch of it supported by NIHBelucidating basic requirements for replicating and packaging influenza virus RNA segments. Moreover, the finding by the UW group, published in the August 3, 1999, issue of the *Proceedings of the National Academy of Sciences,* comes almost 10 years after the first published reports of influenza virus genome manipulation, and almost 3 years after publication of an article describing the generation of recombinant bunyaviruses (segmented genomes of influenza viruses) entirely from cDNA using a recombinant vaccinia virus-driven system. With the production of influenza virus entirely from plasmid DNA, and driven only by the host cell replication machinery, the UW team has finally developed the tools necessary to perform comprehensive examinations of the role of all influenza virus proteins and RNA elements in replication and pathogenesis.

This finding has significant implications for a virus that infects approximately 108 million Americans each year and kills between 20,000 and 40,000 annually, particularly the elderly and those with weakened immune systems. By allowing researchers to manipulate influenza viruses and produce mutations at will, the virus can be engineered to match exactly the strains that may be circulating in the coming season. The current inactive vaccine must be modified each year to account for subtle mutations in the influenza virus. Additionally, in the case of a suspected pandemic, researchers hypothesize that the viruses generated by the new system could be used to rapidly produce an effective, weakened live-virus vaccine, which could induce a more complete immune response, and could selectively produce immunity in targeted areas of the body, such as the nasal cavity or respiratory tract. Instead of involving subtle mutations, viruses that cause pandemics involve new subtypes of influenza and development of a vaccine against a new subtype of influenza can take months.

The new system may also aid in the development of protective measures against other pathogens. By genetically manipulating the flu genome, proteins from other pathogens could be safely introduced to the body's immune system, thus creating a multipurpose vaccination tool out of mutant flu virus.

More broadly, researchers have speculated that this method of manipulating the genetic pattern of the flu virus could be used as a vector to deliver gene therapy. For example, by inserting a curative gene into the flu virus and injecting the virus into a patient, the virus could potentially infect cells with genes capable of reversing a disease process. The same principle may one day be applied for anti-cancer therapy. Based on this exciting avenue of research, influenza may one day be viewed as a useful organism rather than a deadly microbe.

NevirapineBA Global Weapon to Battle Maternal-to-Infant HIV Transmission

HIV/AIDS is a truly global health threat. However, now, for the first time, there is a potent and relatively inexpensive means of reducing the incidence of HIV/AIDS infection in one of the most vulnerable populations of allBnewborn babies of HIV infected mothers. In a collaborative effort involving research scientists at the Johns Hopkins University in Baltimore, the University of Washington in Seattle, and the Makerere University in Kampala, Uganda, investigators supported by the NIH HIV Prevention Trials Network (HIVNET) have achieved a stunning breakthroughBa practical means of significantly reducing the rate of maternal to infant HIV transmission. Their tool was a relatively simple oneBa 200-mg oral dose of nevirapine, a non-nucleoside reverse transcriptase inhibitor (a drug which inhibits an enzyme important in HIV replication) given to HIV-infected women in labor and to their babies within 3 days of birth. This regimen reduced the rate of maternal-infant transmission by half when compared to a similar short course of zidovudine (AZT), a result so impressive that NIH announced the findings even before they were officially published. The reason for such haste is clear. In developing countries, this approach may prevent 300,000 to 400,000 newborns from suffering the effects of HIV infection. The U.S. wholesale cost per-birth for treatment of mother and infant is just $4. At last there is a relatively simple and inexpensive regimen that developing countries may be able to use to prevent HIV transmissionBone that does not require a long course of medication, and that can be administered to women even late in their pregnancies.

For years, the regimen used to prevent maternal-infant HIV transmission was AZT and it remains the standard of care in the U.S. Widespread use of AZT in the U.S. is based on the landmark 1994 study, ACTG 076, which found that AZT reduced maternal transmission of HIV by two-thirds when given to HIV-infected women in the second or third trimester and during labor, and to their infants for 6 weeks following birth. The Centers for Disease Control and Prevention (CDC) reported that the number of AIDS cases resulting from maternal-infant transmission decreased 43 percent in the U.S. from 1992 to 1996, most likely due to the provision of AZT to HIV-infected mothers, better prenatal HIV counseling and testing, and changes in obstetrical management.

While AZT therapy is extremely effective in preventing mother-to-infant HIV transmission, it is too expensive and impractical for widespread use in developing countries where many women do not receive prenatal care. NIH and other Public Health Service agencies embarked on a global strategy to assess whether simpler and less costly regimens to prevent maternal HIV transmission would be effective. Part of this effort involved testing shorter-course AZT therapy. In a randomized trial in Thailand, for example, AZT was administered to the mother for 4 weeks late in pregnancy and during delivery, but not to the infant. In 1998, researchers reported that this regimen yielded a 50 percent reduction in HIV transmission in children who were followed to the age of 6 months. When this same regimen was used in a trial in a breastfeeding population in Cote d=Ivoire, the reduction in transmission was 37 percent. This spring a UNAIDS-sponsored PETRA study in Africa showed a 50 percent reduction in transmission at 6 weeks of age when AZT plus 3TC was given to pregnant women for the last 4 weeks of gestation and to the mother and infant for one week after birth. Despite these promising advances, widespread utilization of

these regimens in most developing countries has not occurred because the regimens still are too costly and they depend on a more sophisticated infrastructure of prenatal care than usually exists in such areas.

While investigators researched more feasible means to prevent perinatal transmission, HIV was evolving into a global epidemic. At the end of 1998, about 1.2 million children under age 15 were living with HIV/AIDS worldwide, and about 3.2 million children under 15 had already died from HIV/AIDS or associated causes. Sub-Saharan Africa has been particularly hard hit; about 30 percent of women in urban, sub-Saharan Africa are infected with HIV, and approximately 25 to 35 percent transmit the virus to their infants. About 1,800 HIV-infected children are born each day in developing countries. A key to mitigating the AIDS pandemic, therefore, was to develop affordable interventions for developing countries.

To develop a safe, effective, and affordable regimen to prevent maternal-infant HIV transmission, NIH took the lead in initiating HIVNET 012. Under this double-blind controlled study (treatment identity concealed from both doctor and patient), the researchers compared the safety and efficacy of AZT and nevirapine administered late in pregnancy. Women in Uganda were randomly assigned either to oral nevirapine at the onset of labor, followed by an oral dose given to their infants within 3 days of birth, or to AZT at the onset of labor and every 3 hours thereafter during labor. The infants born to mothers in the latter group were given AZT twice daily for the first week after birth. The results were unexpected. Nevirapine was significantly more effective than AZT in this population of women with advanced HIV. At 14 to16 weeks, only 13.1 percent of infants who received nevirapine were infected with HIV, compared with 25.1 percent of infants in the AZT group.

The nevirapine regimen is approximately 200 times less expensive than the long course AZT therapy currently used in the U.S. and almost 70 times less expensive than the short course of AZT given to mothers during the last trimester of pregnancyBa fact that makes use of nevirapine feasible worldwide. The nevirapine findings have significant implications for HIV infected mothers in the U.S. as well, especially in populations that have limited access to prenatal care or health care in general and in minority populations that have been particularly stricken by the AIDS epidemic. Of 8,461 cases of pediatric AIDS reported to CDC through December 1998, 58 percent were in African Americans, 23 percent were in Hispanic/Latinos, 17.5 percent were in non-Hispanic Caucasians, and 5.33 percent were in other race/ethnic groups.

Among nevirapine's advantages are that, in contrast to the AZT regimen, nevirapine has the potential to provide last-minute HIV prevention for the babies of pregnant women who do not know their HIV status until they are admitted to a health care facility after beginning labor. In addition, nevirapine is stable during storage at room temperature (a plus when considering the lack of refrigeration equipment in some developing countries), it is rapidly absorbed and transferred across the placenta to the infant, and it breaks down in the body very slowly, thus ensuring protection against HIV exposure during the birth process.

NIH is continuing long-term follow-up of both the mothers and infants in HIVNET 012 for 18 months to assess late-stage drug toxicity, as well as long-term survivalBparticularly in light of the

fact that HIV can be transmitted through breastfeeding in the first few months after birth. The NIH-funded researchers also will embark upon a follow-up study to examine the efficacy of nevirapine administered to the mother during labor and to the infants for a longer period of time. In the U.S. and Europe, a separate study is being conducted to determine whether adding nevirapine to the standard AZT treatment regimens carries any added benefit in preventing perinatal HIV transmission.

With the introduction of nevirapine, the international collaboration of NIH researchers has produced at least one weapon that can be used worldwide to battle neonatal HIV transmission. However, the advent of nevirapine only lessens, but does not eliminate, the treatment-cost barrier that prevents most developing countries from intervening to decrease mother-to-child transmission of HIV. Moreover, the treatment-cost barrier is only one obstacle to adoption of interventions. The cost of other limiting factors, such as HIV counseling and testing, also needs to be considered. If nevirapine continues to be shown to be safe, it could potentially be given to all women in labor who live in areas of high HIV prevalenceBeven women without a confirmed HIV diagnosis. Barring that outcome however, implementation of the nevirapine intervention will require HIV counseling and testingBservices that imply a health care infrastructure that may be beyond the means of many developing nations.

Preventing Cervical Cancer

The prevention of cervical cancer is one of the major public health success stories of the twentieth century. At the center of this story is the National Institutes of Health (NIH), where researchers have helped to unravel the causes of the disease, have presented epidemiologic proof of the causal link between the sexually transmitted human papillomavirus (HPV) and cancer, and are now well on their way to developing the means to prevent cervical cancer in a majority of women.

Success in controlling cervical cancer has important implications for women around the world. Despite advances in the detection of cervical cancer (most notably the Pap smear) and its treatment, this disease remains the second or third leading cause of cancer death in women worldwide, and exacts a devastating toll in developing nations. In the United States, an estimated 12,800 cases of invasive cervical cancer will be diagnosed in 1999, and approximately 4,800 women will die of their disease. Cervical cancer is twice as common among African American women as in white women, because of an excess in older African American women.

The story of our understanding of cervical cancer and its primary cause, HPV, is intriguing. It involves prostitutes, nuns, and a group of second wives, as well as generations of dedicated researchers. Almost a hundred years ago, epidemiologists began to note a curious phenomenon: cervical cancer was common in prostitutes, but extremely rare in nunsBwith the exception of nuns who had been sexually active before entering the convent. They also observed that the rate of cervical cancer was alarmingly high among women who were married to men whose first wives had died of cervical cancer. From these clues, scientists deduced that cervical cancer was caused by a sexually transmitted agent. Several agents were investigated, including syphilis and herpes. It was not until the late 1970s, however, that German researchers identified HPV, long known to cause both cutaneous and genital warts, as the agent in question.

In the 1980s, building on the work of the German researchers, NIH intramural researchers were instrumental in identifying the mechanism by which HPV causes cervical cancer when they found that the viral proteins E6 and E7 induce abnormal cell proliferation and tumor development. Meanwhile, NIH-funded epidemiologic studies in different populations around the world were confirming a causal link between cervical cancer and HPV infection.

Today, papillomaviruses are well established as cancer-causing agents; research has shown that HPV infection is implicated in over 90 percent of cervical cancers. Of the more than 70 known types of HPV, over 30 cause genital infections. About 15 types of HPV are known to cause cancer.

HPV infection is extremely common; more than one in five sexually active young women are infected. Currently, there is no effective treatment for infection with HPV. The overwhelming majority of HPV infections resolve spontaneously, but for reasons that are not yet fully understood, some progress to invasive cervical cancer. For these reasons, research on HPV and cervical cancer in the 1990s has turned to two new areas: the identification of factors that may

contribute to the development of cervical cancer in HPV-infected individuals (these may include smoking and immune status), and the development of a vaccine against HPV infection.

Developing a safe and effective HPV vaccine could have an enormous public health impact in the U.S. alone; such a vaccine has the potential to save thousands of lives and billions of dollars in screening and health care costs each year. The NIH intramural program, in collaboration with industry, is actively working on the development of a vaccine that will prevent HPV infection and, by extension, cervical cancer. Development of a vaccine has been particularly challenging for several reasons. First, because there are so many types of HPV that can cause cervical cancer, and immunity to one type does not confer immunity to others, a successful vaccine will have to be polyvalentBthat is, it will have to target more than one type of HPV. However, a single HPV typeBHPV-16Bcauses over half of all cervical cancers, and three more types cause an additional 30 percent. Therefore, a vaccine targeted to those four types potentially could prevent 80 percent of cervical cancers.

Another problem researchers have faced is that the virus cannot be grown in culture, and therefore creation of a typical attenuated vaccine (a vaccine composed of a crippled virus incapable of causing infection) has proven impossible. Researchers resolved this problem by developing test vaccines using virus-like particles (VLPs), which consist of the major proteins that coat HPV=s outer shell. VLPs developed at NIH are currently licensed to researchers around the world for their own vaccine efforts.

Today, in addition to the studies taking place in the NIH intramural program, there are a number of HPV prevention vaccines that have either reached the earliest stage of human studies. Several chimeric vaccines, which might treat existing HPV infection as well as prevent recurrence, are also currently under study in NIH-sponsored clinical trials.

The story of cervical cancer is a story of excellence in all areas of scienceBfrom population-based studies, to the laboratory and the discovery of the viral proteins that transform normal cells into cancer, to the clinic, where a preventive vaccine will soon be tested. Thanks to decades of productive scientific effort, the burden of this all too common disease promises to soon be reduced substantially.

Using Tamoxifen to Prevent and Treat Cancer

The journey of scientific discovery is neverending, and demands both perseverance and collaboration among researchers and clinicians in order to reach its milestones along the way. This was true in the more than 30-year process of discovery and development of tamoxifen. First developed as a breast cancer treatment, tamoxifen now has been proven to help decrease the risk of breast cancer in women at high risk for developing the disease. The discovery of tamoxifen=s dual role was fostered by the dedicated efforts of many researchers around the world who pursued the use of tamoxifen as a treatment and ultimately recognized its potential for breast cancer prevention, and by the efforts of thousands of patients who volunteered for clinical trials testing tamoxifen.

Tamoxifen, first discovered in 1962, is an anti-estrogenBa substance that stops estrogen from working in specific tissues by preventing the hormone from docking in estrogen receptors found in these tissues. Because of this activity, tamoxifen was first tested as a contraceptive; however, women in the clinical trials who took tamoxifen remained fertile.

Realizing that tamoxifen was not an effective contraceptive, scientists looked for other ways the compound could be used. Through these investigations, they discovered that tamoxifen=s anti-estrogen activity appeared to be selective: it only stopped estrogen from working in certain tissues, such as breast tissue. Knowing that estrogen must bind to its receptors in breast cancer cells to promote tumor growth, and that tamoxifen prevents estrogen from reaching its receptors, scientists began to wonder if the drug might stop breast cancer growth. Therefore, researchers began looking at the drug=s ability to combat the growth of human breast cancer cells in animals, as well as in cancer cells grown in the laboratory. In both settings, tamoxifen successfully robbed the cancer cells of the estrogen they needed for tumor growth. These results led to testing of tamoxifen as a treatment for patients with advanced breast cancers. These first clinical trials were successful, and in 1977, the Food and Drug Administration (FDA) approved tamoxifen for therapy of advanced breast cancer.

Tamoxifen=s success as a treatment for advanced breast cancer fueled many scientists= desire to continue looking for new ways to use the drug to help cancer patients. Tamoxifen was next tested with success as an adjuvant therapy, a treatment given following surgery. Its success as an adjuvant therapy and in treating women with lymph-node involvement led to FDA approval of tamoxifen=s use for these patients in the early 1980s.

As the results of the different trials were reported, the sharing of information among researchers in the laboratory and clinic became critical to refining the design of new trials and uncovering trends in the data. When this growing pool of data was analyzed, three themes began to emerge: women who received tamoxifen had increased rates of survival; women who took the drug had fewer recurrences of cancer; and, it appeared that tamoxifen could decrease the risk of getting another cancer in the opposite breast. In addition, studies in animals showed that tamoxifen could prevent breast cancer.

The results in women with breast cancer suggested that tamoxifen could prevent new breast cancers. But could the drug prevent breast cancer in women who had never been so diagnosed? In 1992, the National Surgical Adjuvant Breast and Bowel Project (NSABP) launched the NIH-funded Breast Cancer Prevention Trial (BCPT) to find out.

In this landmark trial, over 13,000 women at high risk for developing breast cancer volunteered and were randomly assigned to receive either tamoxifen or a placebo. In 1998, the historic results were announced: the data showed that tamoxifen reduces the rate of developing primary breast cancer by 49 percent in women who are at high risk for developing the disease. Potentially severe side effects, such as an increased risk of developing endometrial cancer in women over age 50, and a risk of developing blood clots in the major veins and lungs (similar to hormone replacement therapy), were noted. After noting the observed benefits and side effects, in October 1998, the FDA approved the use of tamoxifen to reduce the risk of breast cancer in women at high risk.

Tamoxifen=s story has not yet come to a close. Researchers are already creating and testing a second generation of breast cancer prevention agents, such as raloxifene, which may help prevent the disease without some of tamoxifen=s potential side effects. In 1999, the NSABP launched the Study of Tamoxifen and Raloxifene (STAR), a trial that is comparing the two drugs= ability to prevent the onset of breast cancer in high-risk, post-menopausal women, as well as comparing the side effects of the two drugs. Approximately 22,000 women will participate in this important study.

As we continue our search for effective methods of preventing breast cancer in all women, we can mark the discovery and development of tamoxifen as a major milestone in medical history. Because of tamoxifen=s unprecedented success at lowering the risk of getting breast cancer, the development of tamoxifen has established a new avenue of prevention research that should continue to foster prevention discoveries and successes well into the future.

Optimal Calcium

In 1989, the recommended dietary allowance (RDA) for calcium for adolescent females was calculated to be 1,200 mg per day. The National Research Council=s RDA Subcommittee determined this amount by extrapolating data from adult, not child-based, calcium studies because so few studies of child calcium requirements had been conducted. Since then, data from key calcium metabolic studies supported by NIH, including some large-scale studies of calcium requirements in children, have resulted in an increase in recommended levels of calcium intake for all ages.

Calcium is needed for hearts, muscles, and nerves to function properly, for blood to clot, and to prevent the bone-thinning disease known as osteoporosis. As early as 1994, when the NIH Consensus Development Conference on Optimal Calcium Intake was held, it was recommended that young adult women Bup to age 24 Bshould ingest 1,200-1,500 mg of calcium per day to build a better skeleton and preserve it throughout life.

The data used for setting adequate intakes for children 9 through 18 years of age are derived from careful and innovative metabolic studies estimating the intakes necessary to achieve maximal calcium retention in the body. NIAMS has supported several studies of calcium in young girls, including ACamp Calcium,@ the purpose of which is to find out how much calcium growing girls need to get in their diets so that they can develop the strongest possible bones.

Studies like these have led to a recommended increase in the calcium intake for 9- and 10-year-old children from 800/mg/day (1989 RDA) to 1,300 mg/day and for 11- to 18-year-old children, an increase from 1,200 to 1,300. Researchers have discovered that the period before puberty is when the most rapid bone acquisition occurs; after that the body=s ability to retain calcium starts to decline. Achieving optimal peak bone mass is essential to preventing osteoporosis in later life.

Other studies, long-term, have also had a major impact on the field of calcium nutritional physiology. Since the late 1960s, NIH investigators have followed a cohort of Catholic nuns from early premenopause up through their early seventies. Results emanating from this study have described changes in calcium balance with age, hormone status, and vitamin D intake. They have also contributed to our understanding of calcium absorption from different food sources and from different types of supplements. This study and others indicate that adequate calcium intake may prevent bone loss, decrease the prevalence of osteoporosis and prevent fractures in the elderly. Accordingly, the RDA for calcium for those over age 50 has been increased from 800 mg to 1,200 mg.

Determining optimal levels of calcium intake is a continuing story. As more data are amassed, guidelines may be further refined. The largest study ever conducted is now under way as part of the NIH Women=s Health Initiative. The results of this study, which will show what can be achieved with calcium and vitamin D supplements, and an upcoming NIH Consensus Development Conference on Osteoporosis could lead to new public health initiatives to optimize the intake of nutrients essential to maximizing peak adult bone mass and minimizing bone loss in later years.

Exercise: A Fountain of Benefits

As the 16th century explorer Juan Ponce de Leon discovered, the fountain of youth does not exist. Now, scientists of the 20th century have discovered an accessible source of benefits that help people feel younger and stay healthier--exercise. Exercise can help prolong healthy life and improve the quality of that life, especially in later years. Exercise benefits both the body and mind, with evidence of increased life expectancy, improved mental health, decreased disability, and, most recently, enhanced learning and memory. Unfortunately, older persons have often been encouraged to slow down or take it easy, and are given little encouragement for engaging in vigorous activity. Despite the proven benefits of exercise, many Americans--especially older Americans--are not engaging in regular, sufficient physical activity. The challenge for research is to expand our understanding of the benefits of physical fitness, as well as to identify the factors that motivate and deter people from making exercise a part of their daily routine.

Research links between physical activity and health began in the early 1980s through epidemiologic studies of selected populations. These studies permitted scientists to examine the natural history of physical activity and the impact of lifestyle on health outcomes. One of the earliest results, from the Alameda County Study, showed that, controlling for socioeconomic status and health factors, older people who reported no leisure-time physical activity were found to be at 37% increased risk for mortality as compared to those who reported some physical activity. The potency of lack of exercise as a risk factor was confirmed even for those 75 and older.

Subsequent findings made it clear that older people are not exercising as much as they should to achieve the health benefits possible through regular physical activity. Data from the 1988-1991 National Health and Nutrition Examination Study illustrated how inactivity rates increase as people age and differ between men and women, and among racial and ethnic groups. Women were found to be considerably less active than men, and prevalence of leisure-time inactivity was higher among African-Americans and Mexican-Americans than among Caucasians.

Regardless of differences among people, the good news is that even moderate physical activity can reap important health benefits, and that it is never too late to start adopting healthier lifestyles. In a recent study, physically active older individuals were found to have a two-fold increased likelihood of living the remainder of their lives with no disability compared to sedentary adults. They are also more likely to live to advanced old age and to remain independent in basic self-care activities in the year prior to their deaths. In this study, moderate physical activity included walking and gardening, activities feasible for many older adults. Ground-breaking studies reported in 1994 involving frail nursing home residents from 72 to 98 years old found that a 10-week resistance exercise program approximately doubled leg strength, increased walking speed, improved stair-climbing power, and led to increased spontaneous physical activity, when compared to controls.

Since the early 1990s, several exercise-oriented intervention studies have been conducted to reduce frailty and injuries. Falls are the primary cause of more than 250,000 hip fractures that occur each year among older persons. One intervention strategy produced a 44% lower rate of

falls than a control group. Exercise can also benefit people suffering from a variety of physical ailments, such as osteoarthritis, a common condition that causes pain and activity limitation in older people. For example, the Fitness Arthritis and Seniors Trial tested the long-term utility of aerobic training (walking) and resistance training (weight lifting) in helping older people with knee osteoarthritis maintain their function and quality of life. Participants reported less pain and better function than controls. Studies on the effects of exercise on chronic pain and peripheral arterial disease observed similar positive results, particularly regarding improved pain management.

Studies have begun to identify a link between exercise and increased life expectancy. In one study, higher fitness was associated with lower mortality rates in men aged 20 to 82. The study found that unfit men age 60 and over who later became fit had death rates 50% lower than those who remained unfit. In another study, people who reported moderate to high levels of exercise lived three or more years longer than less active study participants.

Research on the effects of exercise on the body=s neurological function have produced exciting new findings. Animal studies have shown that exercise can enhance generation of brain cells, which may someday mean that replacement of neurons lost through age, trauma, or disease might be enhanced via a prescribed regimen of exercise.

In humans, exercise can attenuate age-related decline in some cognitive skills. The beneficial effect of aerobic exercise is selectiveBit seems to affect only those functions associated with frontal regions of the brain. A recent study examined the hypothesis that increased light aerobic activity would increase scores on tests of planning, scheduling, and short-term memory, and the inhibition of inappropriate responses. Remarkably, previously sedentary adults, age 60 to 75, with small increases in aerobic fitness due to six months of light to moderate walking, showed substantial improvement in these higher thinking tasks. There were no increases in tasks associated with other regions of the brain, such as short-term memory.

Exercise not only helps daytime functioning, but it also helps individuals get a good night=s sleep. Two independent randomized small controlled trials involving older adults with moderate sleep complaints in moderate exercise demonstrated improvements in the quality of sleep. The first study used an intervention of low-impact aerobics and brisk walking for 30 to 40 minutes four times a week over a 16-week period. Compared to a control group, who did not change their physical activity levels, the exercise group had significant improvements in sleep latency (a 50% reduction, about 15 minutes), sleep duration (increase of almost an hour), and quality of sleep.

The second study used an intervention of progressive resistance training of the large muscle groups for about one hour three days a week for 10 weeks. The control group participated in a health-education program. The participants were depressed elders, aged 60 to 84 years. The exercise regimen resulted in subjective improvement of sleep quality as well as a 50% reduction in depression measures.

Work continues on which types of exercise activities and intervention strategies are most effective for initiating and maintaining physical activity within a diverse, aging population.

Evolution of a System for Providing Comprehensive, Coordinated Post-Hospital Care

Business as usual should be an outdated cliche when it comes to health care. Faced with an increase in the prevalence and duration of chronic illnesses and an aging society, the nation=s health care system needs to be flexible and adopt new strategies that successfully deal with the nation=s changing demographics of an older, more ethnically diverse population and a more knowledgeable and demanding public.

The usual way of doing business has been to provide health care in institutional settings, such as the hospital or the nursing home. More recently, advances in science which have been translated into new technological advances have prolonged life and changed acute illness to long-lasting chronic illness. The movement to a prospective payment system and to a managed health care system have resulted in early discharge of patients from the hospital. Often patients return to their residence with little follow-up professional care or information about their conditionsB which do not necessarily improve once they leave the hospital. Patients may still be at considerable risk, and as the acute disease becomes chronic disease, they face both physical and emotional health problems. Because the setting for post-hospital care is the home, demands and costs for long-term, complex care of multiple illnesses are increasingly being met by family caregivers with varying expertise.

Clinical research has uncovered a new strategy for doing the business of health care that has demonstrated effectiveness in a number of situations and is in sharp contrast with current practice. The strategy is called the transitional care model, which has several unique features. Care is provided at home or in the hospital by advanced practice (master=s prepared) nurse specialists with clinical knowledge and skills matched to their patient populations. Comprehensive discharge planning is developed by the nurses for each patient group and includes assessments of their needs outside the hospital and follow-up in the home with visits and telephone contacts. Because patient care is extended across hospital and home setting by the same advanced practice nurse, with physician consultation and backup, continuity is maintained during the transition period.

The model has been tested in many patient populations and geographic locations, including low birth weight infants in the first year of life, middle aged women undergoing hysterectomies, and older adults with heart failure. Compared to the usual health care, the transitional care model prevents both rehospitalizations and time in the hospital, improves patient satisfaction, and reduces total health care costs.

Findings from a recent randomized trial of older adults with common medical and surgical problems illustrate what the transitional care model has to offer a patient population that is expected to grow and consume an ever larger percentage of the health care dollar. The study=s participants were reflective of the situations of many older peopleBfrail individuals at risk for poor health. They were often were living alone or with inadequate support systems and had multiple chronic health problems, including depression. They were moderately to severely impaired in performing activities of daily living, and had a history of frequent hospitalizations and difficulty adhering to treatment regimens.

Study findings revealed that six months after discharge, only 20% of the intervention group was rehospitalized, compared to 37% of controls, and only 6.2% had multiple hospital readmissions versus 14.5% for controls. Per-patient days in the hospital were fewer for the intervention group B 1.53 versus 4.09 for controls, and the costs of post-discharge health services were about $3,000 lower per patient in the intervention group. When one considers the number of older people hospitalized each year with similar conditions, the benefits to patients and savings to Medicare would be impressive if the transitional care model were to be widely and routinely applied.

The evolution of the transitional care model was stimulated by several other events occurring simultaneously. The prospective payment system (DRGs) in Medicare/Medicaid began in the mid-1980s. This factor, interacting with others, resulted in quicker discharge of patients from high cost hospital care. Home health care and care in settings other than hospitals were becoming common. Separately, by the end of the 1990s, a growing supply of advanced practice nurses prepared at a master=s degree level could prescribe and treat in most States. And as treatments became more complicated and involved powerful drugs and surgery, more information was needed by patients and their caregivers.

The transitional care model has leveraged investment of NIH research dollars and has prompted evaluation of its effectiveness both by the Health Care Financing Administration and managed care in the private sector. Generalized consumer demand for comprehensive, coordinated care offered by the model is emerging, although slowly, since populations where the model was originally applied were often poor and less likely to voice their satisfaction. Transitional care is attracting considerable interest in the health care field, however, particularly among health maintenance organizations, because of the model=s potential to improve quality of life during and after illness at substantial reductions in cost.

The model is next being applied to older adults with congestive heart failure, a very common reason for admission and multiple readmissions to hospital. Lessons learned from this model have implications for people of all ages with chronic diseases or conditions and their families.